Exploring heart and mind of social cognition: A multimodal perspective on socio-cognitive functions in individuals with and without epilepsy

Thesis (cumulative thesis)
presented to the Faculty of Arts and Social Sciences
of the University of Zurich
for the degree of Doctor of Philosophy

by
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Accepted in the spring semester 2018
on the recommendation of the doctoral committee:
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Zurich, 2018

Summary

Social bonds lie at the heart of our daily lives, yet assessing the socio-cognitive functions needed to maintain social relationships is an unresolved challenge in social neuroscience. In line with advances in neuroimaging, social cognition is nowadays investigated from a network perspective instead of focusing on single brain regions. This offers a new approach to examine network alterations which are a potential cause for socio-cognitive deficits in many clinical conditions such as epilepsy. In study one, alterations in the functional network underlying emotion perception were investigated in mesial temporal lobe epilepsy. Comparisons between affected and healthy individuals revealed widespread network disruptions associated with mesial temporal lobe epilepsy, indicating a functional de-coupling of the mesial temporal lobe. Extending the network perspective to the autonomic nervous system, the interplay of central nervous and autonomic processes can be used to study the bodily component of social cognition. In study two, changes in heart rate as part of the physiological adaptation during emotions were examined in a life-like setting. Heart rate trajectories during a disaster motion picture were analysed, which revealed interindividual diversity of trajectories and a significant link between changes in heart rate and empathy. In sum, this thesis contributes to a deeper understanding of social cognition on the neural, physiological and behavioural level.

Zusammenfassung

Zwischenmenschliche Beziehungen stehen im Zentrum unseres Lebens, doch die Erfassung der zur Gestaltung von Beziehungen notwendigen sozio-kognitiven Funktionen stellt eine ungelöste Herausforderung für die sozialen Neurowissenschaften dar. Basierend auf Fortschritten in der Bildgebung fokussiert die Forschung zur sozialen Kognition auf Netzwerke anstelle einzelner Hirnregionen. Dies bietet neue Herangehensweisen um Netzwerkveränderungen, die sozio-kognitiven Defiziten bei Erkrankungen wie Epilepsie zugrunde liegen können, zu untersuchen. Studie eins dieser Arbeit erforschte Veränderungen des Netzwerks zur Wahrnehmung emotionaler Gesichtsausdrücke bei mesialer Temporallappenepilepsie. Ein Vergleich zu gesunden Personen zeigte umfassende Netzwerkdefizite bei Betroffenen auf, was für eine funktionelle Entkopplung des mesialen Temporallappens spricht. Weitet man die Netzwerkperspektive auf das autonome Nervensystem aus, kann das Zusammenspiel zentralnervöser und autonomer Prozesse zur Erforschung der körperlichen Komponente der sozialen Kognition genutzt werden. Studie zwei untersuchte Herzratenveränderungen als Teil physiologischer Anpassung bei Emotionen in einem alltagsnahen Setting. Analysen der Herzratenverläufe während eines Katastrophenfilms zeigten grosse interindividuelle Unterschiede der Verläufe sowie eine bedeutende Rolle der Empathie auf. Insgesamt trägt diese Arbeit zum Verständnis sozialer Kognition auf neuronaler, physiologischer und behavioraler Ebene bei.

Acknowledgements

First and foremost, I want to thank Prof. Hennric Jokeit for providing me the unique opportunity to write my thesis at the Institute for Neuropsychological Diagnostic and Imaging of the Swiss Epilepsy Centre. Hennric, thank you for being an inspiring and supportive supervisor throughout the last three years. The appreciative and ambitious atmosphere you spark within your team enabled me to develop and implement ideas, to err and improve, and to grow professionally and personally. I highly value the extensive time and thought you invested in the progress of my thesis and am grateful for the many fruitful discussions we shared. Your extensive knowledge helped me to see new perspectives and taught me to think big. Thank you for trusting in me and for allowing me to be independent and under close and benevolent guidance at the same time.

*****

My sincere thank goes to Prof. Martin Meyer for encouraging me to take on the challenge of a PhD and for always having strong interest and faith in my work. I appreciated the opportunity you provided to present my projects in your research colloquium and always enjoyed our discourse.

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I want to thank Prof. Birgit Kleim for her readiness to join my PhD committee in a late phase of my work. I am grateful for your acceptance and appreciate your contribution to the final assessment of my thesis.

*****

My gratitude also goes to Dr. Angela Müller for providing training in fMRI analyses. Angela, your persistence on accuracy and your critical feedback improved my methodological skills immensely and laid ground for the first publication of my thesis. Your passion for neuroimaging and your intrinsic curiosity about brain networks had a strong impact on me.

*****

Warmest thanks go to my PhD fellows and friends Esther Spirig and Lorena Kegel. Collaborating with you turned the last three years into an overwhelming scientific adventure and enriched every aspect of my work. I appreciate your contributions to our shared work, our many discussions and your constant willingness to provide feedback on manuscripts. Esther, thank you for all the effort you put into the success of our shared projects, for introducing me to the many caveats of study designs and ethics applications and for the countless hours we

spent on data analyses together. Lorena, thank you for your support during data collection, for many nights spent at fMRI examinations and especially for the conceptual contributions to HiK.

*****

I further want to thank my Master students Johanna Büchel, Anaïs Verrey, Barbara Schaer-Rauber, and Marcel Eicher for their enthusiasm and their valuable contribution to our projects. Additionally, my thank goes to all research interns which made it possible to carry out the extensive data collection. Thank you all for actively participating in our group's projects and for your flexibility to work in many projects.

*****

A special thank goes to the clinical team members who encouraged me throughout my PhD. I deeply enjoyed our time together and could not have wished for a more supportive and positive team. Thank you for being open for new ideas and for giving me the opportunity to partake in neuropsychological assessments. Your willingness to apply the NEmo tests in clinical practice motivated me and showed me the daily relevance of my work. Additionally, I want to thank Prof. Hans-Jürgen Huppertz for providing valuable feedback regarding potential incidental findings in our MRI data.

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I want to express my thanks to the Swiss Epilepsy Foundation for supporting my work by the generous funding of my PhD.

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Finally, I want to thank my friends and family on whose love and support I could always count on during the last years. Special thanks go to Sarah for advising me in many scientific and personal matters, to Damaris for sharing the joys and sorrows of a PhD, and to Sabrina for having an unbiased eye on my work and well-being. Thank you, Andreas, for always believing in me and for your unconditional love during these challenging times.

Contents

Abbreviations

ACC	Anterior cingulate cortex
AED	Antiepileptic drugs
ANS	Autonomic nervous system
aSTS	Anterior superior temporal sulcus
AV	Atrioventricular node
BOLD	Blood oxygenated level dependent
bpm	Beats per minute
CAN	Central autonomic network
CVLM	Caudal ventrolateral medulla
DVN	Dorsal vagal neuron
ECG	Electrocardiogram
EEG	Electroencephalography
ENS	Enteric nervous system
EPI	Echo planar imaging
FC	Functional connectivity
FFA	Fusiform face area
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FWE	Family wise error
HC	Healthy control participants
HF	High frequency component of heart rate variability
HRV	Heart rate variability
HS	Hippocampal sclerosis
IBI	Interbeat interval
ICA	Independent component analysis
IFG	Inferior frontal gyrus
ILM	Interomediolateral cell column
LF	Low frequency component of heart rate variability
LF/HF	Ratio between the low and high frequency component of heart rate variability
mPFC	Medial prefrontal cortex
MPRAGE	Magnetization prepared rapid gradient echo sequence
MRI	Magnetic resonance imaging
MTLE	Mesial temporal lobe epilepsy

NA	Nucleus ambiguus
NTS	Nucleus of the tractus solitarious
OFA	Occipital face area
PAG	Periaqueductal gray
PB	Parabrachial nucleus
PFC	Prefrontal cortex
PG	Precentral gyrus
PNS	Parasympathetic nervous system
pSTS	Posterior superior temporal sulcus
RMSSD	Root mean square of successive differences
ROI	Region of interest
RVLM	Rostral ventrolateral medulla
SA	Sinoatrial node
SDNN	Standard deviation of normal-to-normal intervals
SNS	Sympathetic nervous system
SPM	Statistical parametric mapping
STS	Superior temporal sulcus
TE	Echo time
ToM	Theory of Mind
TPJ	Temporo-parietal junction
TR	Repetition time
VLF	Very low frequency component of heart rate variability

1 Introduction

Our entire lives revolve around social bonds. Establishing and maintaining social relationships highly determines one's physical health and subjective well-being (Helliwell & Putnam, 2004). Although social interactions appear to flow effortlessly, perceiving signals from our social environment and adapting one's behavioural responses accordingly relies on the dynamic interplay of socio-cognitive functions. Social cognition describes the perception and interpretation of affective and mental states of others as well as the generation of responses to these states within a social situation (Green et al., 2008; Van Overwalle, 2009). Despite the high prevalence of socio-cognitive dysfunctions in clinical conditions (Cotter et al., 2018) such as epilepsy (Bora & Meletti, 2016), the field of social neuroscience is challenged by conceptual and methodological discussions.

Conceptually, many facets of social cognition still lack sustainable definitions and models that are shared among scientists (Gendron & Feldman Barrett, 2009; Walter, 2012), which impedes progress in research on social cognition. Still, advances in neuroimaging and psychophysiology promoted our understanding of social cognition and led to a shift in paradigm. Instead of focusing on single brain regions (e.g. the amygdala as "fear centre" of the brain), research turned its focus on whole-brain networks supporting socio-cognitive functions (Pessoa & McMenamin, 2017). Investigating these networks in healthy and clinical populations is an ongoing challenge in social neuroscience.

From a methodological point of view, research on social cognition struggles with a substantial gap between commonly applied experimental settings and the reality of daily live social interactions (Schilbach et al., 2013). Established assessment tools are often based on photographs or stories (Henry, von Hippel, Molenberghs, Lee, & Sachdev, 2016); thus, they do not live up to the wealth of information provided by a natural interaction partner and offer little possibilities for active engagement. Innovative study designs that apply realistic stimuli and are able to evoke emotions are required in order to provide results of high ecological validity. In addition to measures on the behavioural level and neuroimaging, recordings of bodily signals can provide insight into socio-cognitive functions (Critchley, Eccles, & Garfinkel, 2013). The association of emotions and physiological processes has been studied for centuries (Darwin, 1872; James, 1894; Wundt, 1874), yet just current technical developments allow for elaborate statistical analyses of psychophysiological signals.

This thesis strives to advance current conceptual challenges by use of innovative study designs and elaborate methodological approaches which were implemented in two original

empirical publications. Preceding these empirical studies, the daily relevance of socio-cognitive deficits as well as intra- and interindividual determinants of social functioning are discussed in a theoretical study with focus on people with epilepsy. Subsequently, the first empirical study aims to investigate the functional brain network that supports the perception of facial emotional expressions, which are a building block of social interactions (Haxby, Hoffman, & Gobbini, 2000; Jack & Schyns, 2015). A comparison between participants with mesial temporal lobe epilepsy and healthy participants serves to examine the relevance of the functional integrity of the mesial temporal lobe in the observed brain network. The second empirical study focusses on psychophysiological adaptations during emotional experiences. Changes in heart rate, which are part of the bodily component of emotions (Kreibig, 2010), are examined during the presentation of an entire highly emotive[1] motion picture. The study targets the potential for diversity in heart rate responses to emotive stimuli and links changes in heart rate to the participants' predisposition to empathize with others.

In the following section, the theoretical background of these three studies will be presented. After providing an introduction to social cognition (2.1), the neural base of selected socio-cognitive functions will be outlined and integrated from a network perspective (2.2). Subsequently, the role of the autonomic nervous system in social cognition with an emphasis on the heart will be discussed (2.3). With respect to the first empirical study, mesial temporal lobe epilepsy and common deficits in social cognition as well as functional brain alterations will be introduced later (2.4). Methodological considerations on functional magnetic resonance imaging (3.1) and analyses of heart rate (3.2) are provided in the following section before outlining the aims and research questions of this thesis (4). A theoretical study on the intra- and interindividual determinants of social functioning in epilepsy (5) precedes the empirical part and provides a framework for the following two empirical studies (6.1; 6.2). After presenting the two empirical studies, a general discussion consisting of theoretical (7.1) and clinical implications (7.2) as well as limitations and future questions (7.3) is provided. The thesis closes with concluding remarks (7.4).

[1] In this thesis, the terms "emotive" or "emotionally charged" are used to describe a stimulus with the potential to evoke emotions in the observer due to its characteristics and relevance for the observer. Central nervous processes within the observer in response to the emotive stimuli are subsumed under the term "emotional processing", whereas the holistic state of responding to emotive stimuli is labelled "emotional experience". This distinction pays respect to the circumstance that emotions arise from the interaction of the individual with the environment (Gross, 2015) and serves to clarify whether statements are related to the stimuli or the observer.

2 Theoretical background

To start with, an introduction to social cognition in general and its main components is provided. Special emphasis is put on emotion perception from facial expressions and empathy, for these concepts are central to both studies of this thesis.

2.1 Social cognition

Social relationships are of such enormous importance for human survival that they not only dominate our daily lives but also our brain circuits. Although engaging in smooth, dynamic interactions requires a multitude of advanced social skills, most of us handle the complexity of the social environment seemingly effortlessly (Hari, Henriksson, Malinen, & Parkkonen, 2015). The functions needed to successfully interact with others are subsumed under the term of social cognition. Social cognition is an umbrella term for the variety of brain functions that serve the perception and interpretations of social information such as behaviours, intentions, attitudes, and emotions (Green et al., 2008; Van Overwalle, 2009). Furthermore, inferences from social cognition guide our behaviour by modulating cognitive domains such as memory, attention, motivation or decision-making (Adolphs, 2001). Failing to perceive and understand the social signals of others can have a detrimental effect on one's social integration in major life domains (Steiger & Jokeit, 2017) and therefore also on quality of life (Szemere & Jokeit, 2015). Given the complexity and behavioural relevance of socio-cognitive functions, it is hardly surprising that deficits can be observed in many psychiatric as well as neurological conditions (e.g. Ladegaard, Larsen, Videbech, & Lysaker, 2014; Milders, Fuchs, & Crawford, 2003).

In the following sections, different socio-cognitive processes will be described in more detail. To begin with, emotions as the building blocks of social cognition will be defined (section 2.1.1). Subsequently, basic socio-cognitive processes of emotion perception, especially based on facial emotional expressions, will be described (section 2.1.2). After that, advanced socio-cognitive functions will be distinguished (section 2.1.3). Finally, the current clinical practice to assess these functions will be discussed briefly (section 2.1.4).

2.1.1 Emotions

Emotions are signposts that guide us through the social environment. They enrich our daily lives with meaning, allow us to express and perceive the internal states of others and ourselves, and enable us to cope with environmental demands and challenges (Cacioppo, Berntson, Larsen, Poehlmann, & Ito et al., 2000). There is hardly a psychological concept that

is equally ubiquitous and at the same time so loosely agreed on as emotions. Lindquist et al. (2013) even stated that "the emotion debate has been fought like a series of battles", taking off with Darwin's ground-breaking work *Expressions in man and animals* (1872) and the following discourse on the origin of emotions with influential contributions of scientists such as William James and Carl Lange (Lange & James, 1922) or Stanley Schachter and Jerome Singer (Schachter & Singer, 1962), whose roles will be presented in section 2.3.4 with emphasis on the bodily components of emotions. An exhaustive overview covering functionalistic and constructivist approaches as well as appraisal theories goes beyond the scope of this thesis, but is provided by Gendron & Barrett (2009). Nowadays, there is overarching consensus that emotions emerge from the continuous comparison of challenges and opportunities arising from the environment and one's own current needs, previous experiences and personal goals (Cacioppo et al., 2000; Schirmer & Adolphs, 2017; Thayer & Lane, 2000). Within this dynamic interplay of the individual and its environment, emotions are a multifaceted phenomenon composed of orchestrated changes in subjective experience, behaviour, cognition and peripheral physiology (Gross, 2015). Thus, they involve whole-body adaptations of the central and the autonomic nervous system with the aim to fulfil one's needs in a specific situation (Critchley et al., 2013).

The inconsistent use of the term emotion and related concepts of affect, mood and feelings complicates the debate and consequentially research on emotions. Affect can either be understood as a precursor of more complex emotions (Schirmer & Adolphs, 2017), but is also used as an umbrella term for all the aforementioned concepts (Gross, 2015). In this thesis, the latter position is adopted in order to be consistent with the general use of "affective processing" in current research. Moods differ from emotions in duration and orientation: They can last for hours and are not oriented towards a specific stimulus, whereas emotions range from seconds to minutes and occur within a situation with relevance to the individual and it's needs and goals (Ekkekakis, 2013; Gross, 2015). The term feeling corresponds to the subjective experience of an emotion and describes the inward-oriented conscious perception of one's own emotional state (Levenson, 2014). In contrast, emotions consist of an expressive and behavioural component and thus produce visible signals for others (Cacioppo et al., 2000; Schirmer & Adolphs, 2017).

Although the exact mechanisms underlying emotions have yet to be discovered, their signal function in social situations is indisputable. Perceiving and understanding emotions of others efficiently is the fundamental element of social cognition (Mitchell & Phillips, 2015; Van Overwalle, 2009) and is covered in the following section.

2.1.2 Perception of facial emotional expressions

Emotions find expression in many behaviours; a face twisted in disgust, hands trembling with fear, devastated sobs or joyful laughter, a furious grip. These expressions, whether intended by the sender or not, serve as communicative signals and allow others to infer hidden mental states (Gallese, Keysers, & Rizzolatti, 2004; Schirmer & Adolphs, 2017). The identification of such salient verbal and non-verbal cues of other people's emotions in the social environment is defined as emotion perception (Mitchell & Phillips, 2015). Emotion perception requires the dynamic integration of information across multiple sources such as another person's facial expression, eye gaze, body posture and movement, speech or vocalization, touch and also subtle cues like pallor or blushing of the skin (Kret, 2015). With respect to the significance of faces for the expression of emotions in our daily lives (Haxby et al., 2000) and due to the strong reliance of the paradigms applied in the empirical part of this thesis on visual cues, the following sections will focus on visually presented emotional cues conveyed by faces.

The face is possibly the most powerful tool to transmit dynamic patterns of socially relevant signals and communicate emotions. Newborns already show a preference for stimuli that resemble human faces (Simion & Giorgio, 2015), and until adulthood, healthy individuals refine their perceptive functions so that a brief glimpse already reveals a wealth of information regarding a person's identity, age, gender, ethnicity and physical health (Jack & Schyns, 2015). However, most time is not spent dwelling on a person's identity but rather on their facial emotional expression (Haxby et al., 2000). By contraction of the facial muscles, a multitude of emotional expressions can be displayed in varying intensity and in quick succession (Ekman et al., 1987). This capability turns the face into the major source of information in social interactions (Hari et al., 2015). Inferring said emotional states from a face requires multiple processing steps covering attention for as well as the perception and interpretation of the facial expression (Mitchell & Phillips, 2015).

Facial expressions can be classified with the Facial Action Coding System (Ekman & Friesen, 1976), which describes action units of one or multiple facial muscles that give rise to emotional expressions. Building on this system, Ekman and Friesen proclaimed the existence of universal emotional expressions labelled basic emotions (Ekman et al., 1987). These expressions are assumed to be shared among all human cultures (and to some degree also further mammals) and should express evolutionary shaped emotions such as fear, anger, disgust, joy, sadness and surprise (Ekman & Cordaro, 2011). Although their existence and universality has been questioned by many (e.g. Barrett, 2006), and though humans are without a doubt able to produce far more fine-grained facial expressions, basic emotions have served as a versatile

model in social neuroscience. Still, there is a large gap to bridge in research to meet the variety and dynamics of human facial expressions in real life.

In this thesis, emotion perception has been defined as the identification of socially relevant verbal and non-verbal cues in another person in order to infer their emotional state. Facial emotional expressions serve as the major source of social information, yet emotions can also be expressed by posture, motion, vocalization or touch. Accurate perception of these signals is the essential building block for advanced socio-cognitive processes which will be outlined in the following section.

2.1.3 Empathy and Theory of Mind

The mere perception of emotional signals in other individuals is not sufficient to adequately engage in beneficial social interactions. In addition, it is vital to figuratively put ourselves in the shoes of others to participate in smooth social interactions. This requires higher socio-cognitive processes, mainly empathy and Theory of Mind (ToM) skills (Mitchell & Phillips, 2015). The two concepts will be defined and discussed in this next section with a main focus on empathy due to its importance in the second empirical study of this thesis. Brain regions and neural circuits underlying these concepts will be discussed later in this thesis in section 2.2.

Other people have minds with mental states of their own, and their minds differs from one's own mind. Although this notion sounds trivial, the awareness of private and possibly differing mental states is a core aspect of ToM (Premack & Woodruff, 1978). Furthermore, ToM entails the ability to infer these mental states of others, such as their intentions, beliefs, emotions, thoughts and knowledge. These inferences serve the prediction of another person's future behaviour (de Waal & Preston, 2017; Mitchell & Phillips, 2015). In sum, having a theory of mind refers to the cognitive ability to reflect on one's own and other's mind (Baron-Cohen, 2001).

In contrast, empathy can broadly be understood as an affective reaction that occurs as response to the affective state of another human being (Walter, 2012). In their influential definition that was carried on by many colleagues, de Vignemont and Singer (2006) state four conditions that characterize empathy: An individual experiences an affective state (i) that is isomorphic to the affective state of another person (ii) and that is further elicited by observing or imagining the other person's affective state (iii). However, the observer is aware of the fact that the other person and not the self is the source of the experienced affective state (iv). Being emotionally touched in an isomorphic way while maintaining self-other distinction are crucial

aspects that separate empathy from related constructs such as sympathy or emotional contagion (de Vignemont & Singer, 2006). Empathy is not an automatic nor uniform process but is rather modulated by many factors. The experience of empathy towards another person is influenced by the perceived emotional state, the relationship between the observer and the observed person, characteristics of the observer (e.g. personality, age, gender, mood) as well as the surrounding context (Cuff, Brown, Taylor, & Howat, 2016; de Vignemont & Singer, 2006). Additionally, top-down processes such as cognitive appraisal and corresponding emotion regulation shape one's empathic responses (de Waal & Preston, 2017).

The definition of empathy is subject to an ongoing debate that foremost targets the extent to which ToM processes are part of empathy. Many researchers assume an extensive overlap of the two constructs (see Cuff et al., 2016, and Walter, 2012, for discussions). Lamm, Rütgen and Wagner (2017) point out that the imagination of another person's state translates to the process of mentalizing or perspective taking, which are frequently used synonymously to ToM (Frith & Frith, 2003). Accordingly, this facet of empathy has been labelled cognitive empathy by some (e.g. Decety, 2010) because the internal state of another person is inferred by reflecting on their state (Mitchell & Phillips, 2015). Although processes of ToM can be a mean to attain a shared affective state, they are not part of said state (Lamm et al., 2017). Therefore, ToM on its own does not suffice to experience empathy as an "affective fusion with another individual's state" (de Waal & Preston, 2017).

A further point of debate is whether the potential affective and behavioural consequences of empathy (i.e. sympathy, prosocial concern and helping behaviour), should be viewed as part of empathy itself. Zaki and Ochsner (2012) define empathy as a process of vicariously sharing the experiences of another person while also mentalizing about this observed state. Additionally, they identify prosocial concern as a motivational component of empathy. However, empathic sharing of affects does not necessarily induce concern for the other person. Instead, it could equally lead to personal distress and withdrawal behaviour (de Vignemont & Singer, 2006). Furthermore, the motivation to console can arise without the experience of an isomorphic affective state simply from feeling sympathy (Walter, 2012).

In sum, there is widely supported consensus that sharing the affective experience of an observed or imagined other individual represents the core aspect of empathy. This shared state can be attained by mentalizing about the mental states behind an observed affective state, but cognitive perspective taking alone does not qualify as empathic experience. Following de Vignemont & Singer (2006) as well as Lamm et al. (2017), empathy is in this thesis defined as the experience of an isomorphic affective state, which stems from the observation or

imagination of another person's affective state, while distinction between the self and the other is maintained. These core aspects of empathy as well as influence factors and disparate concepts are visualised in figure 1.

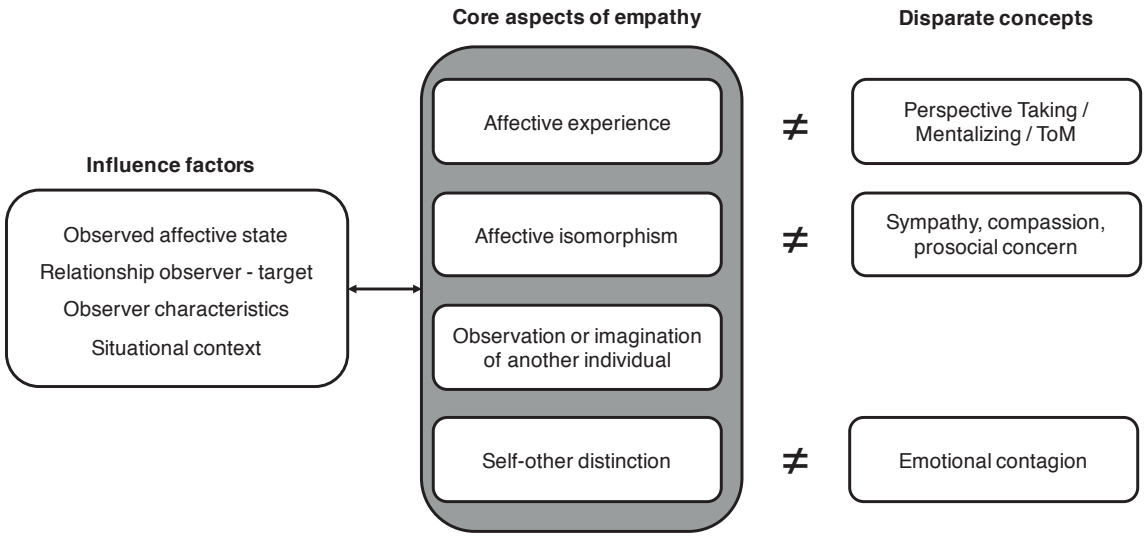

Figure 1. Visualisation of core aspects of empathy based on de Vignemont & Singer (2006) as well as influence factors and disparate concepts.

2.1.4 Clinical practice for testing social cognition

Social cognition is paramount for one's well-being and social integration. Considering the complexity of socio-cognitive functions, it comes as no surprise that socio-cognitive deficits are discernible in many neurological and psychiatric conditions (Cotter et al., 2018; Kennedy & Adolphs, 2012; Martín-Rodríguez & León-Carrión, 2010). In contrast to their frequent impairment, there is an alarming shortage of neuropsychological diagnostic tools and procedures to assess socio-cognitive functions. Social cognition is often neglected in clinical assessments in favour of other domains such as memory or attention (Henry et al., 2016). Currently available tools can roughly be divided into measures of emotion recognition, ToM and empathy.

The most established way to assess the efficiency of emotion perception is to present photographs of emotional facial expressions and ask the patient to identify the expressed emotions by choosing a verbal label. Commonly, black-and-white photographs such as the Ekman and Friesen picture set (Ekman & Friesen, 1976) are used. However, static images

cannot live up to the wealth of social information in real life, and thus alternative procedures closer to one's actual life are necessary (Henry et al., 2016).

Advanced socio-cognitive functions of ToM and empathy are most frequently examined by use of story-based procedures such as Baron-Cohen's Faux-Pas Test (Stone, Baron-Cohen, & Knight, 1998) or Happé's strange stories (Happé, 1994), in which patients are asked to infer the mental states of the stories' protagonists. Alternatively, picture-based (e.g. Reading the Mind in the Eyes Test, Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) or video-based tests (e.g. The Awareness of Social Inference Test, McDonald, Flanagan, Rollins, & Kinch, 2003) can be applied. Results must be interpreted with caution because sensory as well as cognitive deficits can impede test performance, especially in story-based procedures with high cognitive demand (Henry et al., 2016).

Complementary to test procedures administered by physician or psychologist, self-report or third-party-report questionnaires are used to inquire about a patient's perceived socio-cognitive functions (e.g. Interpersonal Reactivity Index, Davis, 1983; Empathy Quotient Scale, Baron-Cohen & Wheelwright, 2004). Although questionnaires can provide valuable insight into the self-evaluation of a person, they yield a high potential for being biased either by a lack of insight, social desirability or even the wish to deceive (Choi & Pak, 2005).

This brief overview of diagnostic tools already reveals the current predicament in the investigation of social cognition. Although some validated tools are available by now (Henry et al., 2016), research is still limited by the range of tests which are not entirely suitable to capture those processes necessary for smooth social encounters in real-life (Stanley & Adolphs, 2013). In addition, socio-cognitive functions often do not find expression in directly observable behaviour or cannot be verbalised appropriately (Cacioppo et al., 2000). Therefore, it is not expedient to assess social cognition entirely on the behavioural level. The reliance of social cognition on distributed brain regions provides the opportunity to approach social cognition based on its neural correlates (Van Overwalle, 2009). Furthermore, physiological adaptations that come along with socio-cognitive processes (e.g. the racing heart beat when in fear) open up another window into social cognition (Critchley, 2005). In order to appreciate this multifaceted nature of social cognition and to include its neural as well as physiological components, research needs to combine behavioural paradigms with further measurement techniques. Insight into the neural base of social cognition has already been brought forward by a wealth of neuroimaging studies, yet we just begin to understand how the brain as a network coordinates affective processing. The current state of research on the underlying neural circuits of central socio-cognitive functions is presented in the next section.

2.2 Neural base of social cognition

Social cognition draws upon the dynamic interplay of behavioural, neural and physiological processes (Critchley et al., 2013; Stanley & Adolphs, 2013). While the behavioural component can readily be observed in daily life, only advances in neuroimaging techniques enabled scientists to study its neural base beyond the conclusions from early lesions studies such as the famous case of Phineas Gage (Harlow, 1868). Investigating the neural circuits supporting social cognition is not only crucial to anticipate and evaluate deficits in individuals with brain lesions, but also to retrace the link between central and autonomic nervous processes discussed in section 2.3. With regard to the main focus of this thesis' empirical part, neural correlates of facial emotion perception and empathy will be outlined.

2.2.1 Brain regions involved in emotion perception from faces

The inference of emotional states that are communicated by facial expressions requires multiple processing steps ranging from basic visual analyses to the extraction of facial features, integration of motion-based information, recognition of the emotional expression and subsequent interpretation of the inferred state (Bernstein & Yovel, 2015). Adapting the influential model of face perception of Haxby and colleagues (2000), a revised neural framework for face processing was recently proposed by Duchaine & Yovel (2015). In this framework, regions involved in face processing are divided into two separate but interacting pathways. The ventral stream is formed by face selective areas in the inferior occipital gyrus, the fusiform face area and the anterior temporal lobe. Via this ventral route, form information regarding invariant features (e.g. sex, age, identity) are processed. The dorsal route spans from the posterior superior temporal sulcus (pSTS) to the anterior superior temporal sulcus (aSTS) and further includes the inferior frontal gyrus (IFG). Regions of the dorsal pathway are involved in the processing of dynamic facial information such as biological motion and expressions, eye gaze and facial motion. According to Duchaine & Yovel (2015), especially functions of the dorsal pathway are essential for social interactions since they support the ongoing processing of dynamically changing input from faces. A schematic overview of this contemporary model of face processing is reproduced in figure 2.

The framework of Duchaine and Yovel (2015) focusses on primary face-selective areas. However, it does not include brain areas that have long been implicated in the processing of facial emotional expressions. These additional areas have been subsumed in the 'extended system of face perception' in the model of Haxby and colleagues (2000). Regarding the perception of facial emotional expressions, they point out the role of the limbic system and

emphasize the involvement of the amygdala and the insula (Haxby et al., 2000). This claim is supported by three meta-analyses on facial emotion perception, who report substantial contribution of the amygdala in the processing of facial emotional expressions (Fusar-Poli et al., 2009; Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Sabatinelli et al., 2011). In fact, fast responses in the amygdala to especially fearful faces have been demonstrated already 74ms after stimulus perception – and thus preceding responses in primary face-selective areas – by use of intracranial electrophysiological recordings (Méndez-Bértolo et al., 2016). Although the anatomical pathway underlying this response is not yet clarified in humans, these findings substantiate the importance of the amygdala for quick responses to visually perceived biologically relevant information (Pessoa & Adolphs, 2010). Additionally, activation of the insula was found for the perception of most basic emotional expressions as well as for neutral faces (Fusar-Poli et al., 2009; Lindquist et al., 2012).

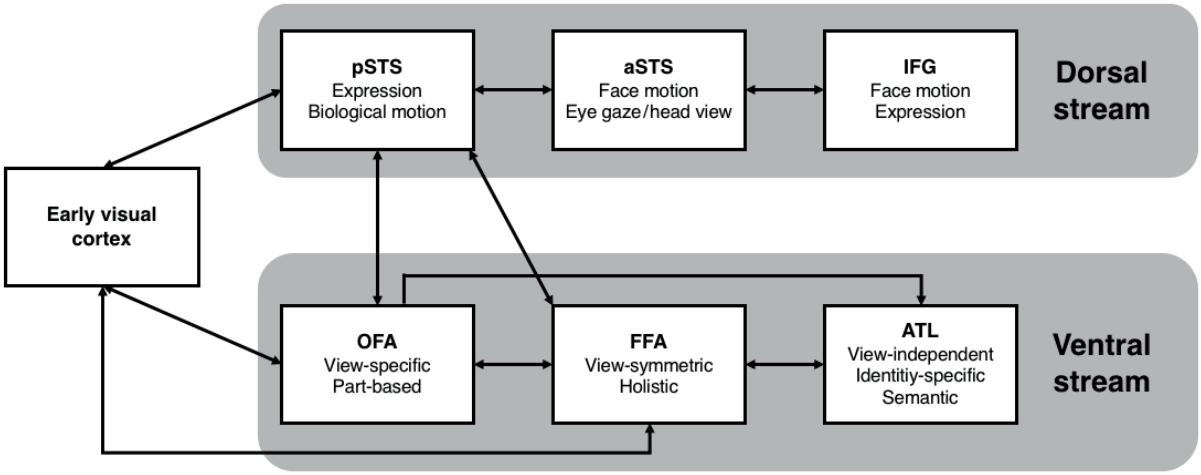

Figure 2. The revised neural framework for face processing with the distinction between the dorsal and ventral stream as proposed by Duchaine & Yovel (2015). Figure adapted from Duchaine & Yovel (2015).

In summary, the processing of facial emotional expressions relies on pathways extending over occipital, temporal, as well as limbic brain regions. Especially the dorsal pathway of face perception (Duchaine & Yovel, 2015) in conjoint activation with the amygdala and the insula underlie the processes necessary to decipher dynamically changing facial

emotional information. The outcome of these processes is crucial for empathy and ToM (Mitchell & Phillips, 2015), whose central underlying brain structures are outlined next.

2.2.2 Brain regions involved in empathy and Theory of Mind

Empathy was defined as the isomorphic sharing of an observed or imagined affective state of another person while maintaining a sense of self-other-distinction (de Vignemont & Singer, 2006). A common assumption in research on empathy is that this affective isomorphism relies on the activation of brain regions that would equally be engaged if the observed or imagined state was experienced first-hand (Preston & De Waal, 2002). The majority of studies that aimed to provide evidence for this shared neural representation used paradigms focusing on pain. Traditionally, brain activity during self-experienced pain was compared with the neural response to observed or imagined pain of others, which is assumed to cause vicarious pain in the observer (Singer & Lamm, 2009). The assumed overlap of neural responses was demonstrated by a meta-analysis of Lamm, Decety and Singer (2011), who showed that bilateral activity in the anterior insula and further activity in the anterior cingulate cortex underlie real pain as well as empathy for pain. These areas could also be reproduced for the empathic sharing of affective states such as fear or sadness instead of pain (Fan, Duncan, de Greck, & Northoff, 2011). These findings indicate that the insula is involved in the representation of one's own but also of other individual's affective states (Bernhardt & Singer, 2012). Lesion studies additionally underpin the relevance of the insula for empathy, but further demonstrate that diffuse brain lesions also have the potential to disrupt one's ability to empathize with others (Hillis, 2014).

Activation of the insula and anterior cingulate cortex has consistently been shown during first-hand and vicarious experiences of pain, yet the neural substrate for an actual bodily sensation – activity in the somatosensory cortices – could not be demonstrated reliably in empathy (Bernhardt & Singer, 2012). In their meta-analysis, Lamm and colleagues (2011) compared activation patterns for story-based and picture-based paradigms of empathy (e.g. hearing about the injury of another person vs. seeing pictures or video clips of an injury). Experiments relying on stories or abstract cues were not associated with activity in somatosensory cortices, whereas picture-based paradigms had the potential to evoke activity in the primary somatosensory cortex. However, the mere perception of tactile or proprioceptive manipulation (e.g. stroking a hand with a feather, gently bending joints) is sufficient to evoke activity of the somatosensory cortices in the absence of any stimuli that would encourage feelings of empathy (Keysers, Kaas, & Gazzola, 2010; Lamm et al., 2011). Therefore, the

somatosensory cortices cannot be considered core regions for empathy but contribute to social perceptive processes in general (Keysers et al., 2010; Lamm et al., 2011). These findings imply a further refinement of the definition of empathy for pain, since they indicate that vicarious pain does not occur with precise mapping of another person's injury but rather on a global level of bodily and affective representations.

Definitions of empathy vary immensely by the degree to which they incorporate cognitive processes, which creates almost a continuum from affect sharing to purely cognitive processes of mentalizing (Walter, 2012). In daily life as well as in paradigms to provoke neural activation associated with empathy, empathy and ToM processes often co-occur and complement each other, yet their neural substrate does not overlap entirely. Neuroimaging experiments posing larger demands on the inference of mental rather than affective states have repeatedly described a core set of brain regions that includes the medial prefrontal cortex (mPFC), the temporo-parietal junction (TPJ), the pSTS and a region in the precuneus and posterior cingulate cortex (Carrington & Bailey, 2009; Van Overwalle, 2009). Especially processes such as the attribution of agency, self-other distinction and perspective taking have been attributed to the TPJ (Abu-Akel & Shamay-Tsoory, 2011; Carrington & Bailey, 2009). In a recent meta-analysis that aimed to differentiate activation patterns for the most commonly applied ToM paradigms, Schurz et al. (2014) could substantiate the key role of TPJ and mPFC across numerous experimental conditions. In contrast to story-based or imagination-based experiments, tasks relying on social animations or photographs showed stronger involvement of the pSTS and the IFG (Schurz & Tholen, 2016).

So far, core structures for empathy as well as ToM have been identified (Lamm et al., 2017; Schurz et al., 2014). Nevertheless, the accumulated evidence of fMRI and lesion studies points out that the complex processes underlying social interactions cannot be ascribed to single brain regions but rather relies on the coordinated activation of these regions in functional brain networks. It is thus essential to adopt a new perspective and investigate the interweaved neural networks of social cognition, which is the central topic of the next section.

2.2.3 Social brain networks

The idea that brain areas are organized into functional networks is by no means a novelty. As early as 1937, Papez (Papez, 1937) proposed a circuit of distributed brain areas that provides the "mechanism of emotion". Today, the emergence and rapid development of techniques such as fMRI make it possible to observe the functional coupling of brain regions in vivo (Fox & Raichle, 2007). The functional organisation of the brain into networks can be

inferred from measures of functional connectivity (FC), which is defined as the temporal coherence of spatially distributed physiological events (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). A methodological introduction to the concept of fMRI and FC is given in section 3.1 of this thesis. In short, analyses of FC allow us to draw conclusions about functional brain networks that can be observed during tasks, but also spontaneous fluctuations of activity in the absence of tasks have received much attention during the last years (Hutchison, Womelsdorf, Allen, et al., 2013). In the absence of an external task, FC is assumed to reflect the brain's organisation in intrinsic functional networks (Buckner, Krienen, & Yeo, 2013). In the context of this thesis, studies on FC can provide insight into the functional networks that contribute to social cognition.

A contemporary view on functional networks supporting social cognition was presented by Kennedy & Adolphs (2012). They propose that no socio-cognitive function can be understood as the output of a single brain region but rather as the result of an efficient interplay of many regions grouped into networks. Furthermore, they propose four partly overlapping functional networks related to social cognition (see figure 3): The amygdala network subserving detection and processing of emotive stimuli, the mentalizing network related to ToM processes, a network associated with the perception and mirroring of actions, and finally the frequently reported empathy network centred on the anterior insula (Kennedy & Adolphs, 2012; Lamm et al., 2017; Stanley & Adolphs, 2013).

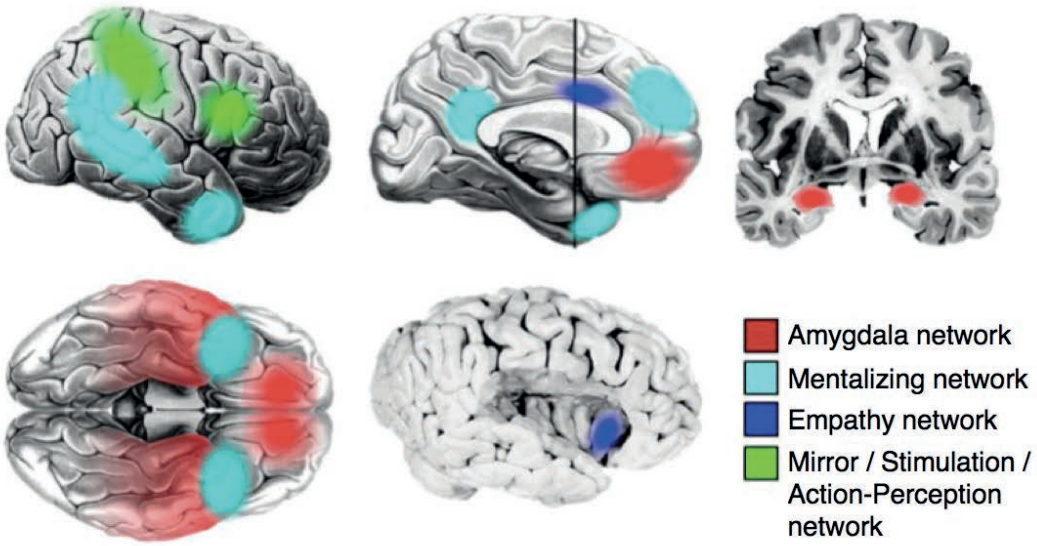

Figure 3. Functional brain networks of human social cognition. Figure adapted from Kennedy and Adolphs (2012).

While the proposed networks of Kennedy and Adolphs (2012) mostly rely on studies on brain activity and not connectivity, research on the intrinsic FC among the respective brain regions supports these functional networks (Amft et al., 2015; Bickart, Hollenbeck, Barrett, & Dickerson, 2012). Kennedy and Adolphs (2012) already point out that the assignment of single brain regions to only one socio-cognitive network would be an oversimplification. This note of caution is substantiated by Bickart and colleagues (Bickart et al., 2012; Bickart, Dickerson, & Feldman Barrett, 2014), who demonstrated that the amygdala is a core structure in at least three differentiable intrinsic functional networks related to perception, affiliation behaviour and aversion behaviour. While the perception and affiliation networks closely resemble the amygdala network proposed by Kennedy and Adolphs (2012), Bickart and colleague's (2012) aversion network corresponds to their empathy network encompassing the anterior insula and the anterior cingulate cortex. The importance of the conjoint activity of these structures is further highlighted by Touroutoglou et al. (2015), who investigated functional networks associated with the perception of basic emotions. Instead of emotion-specific brain networks, they report a shared network underlying the perception of negative facial emotional expressions that closely resembles the aversion network of Bickart et al. (2012).

The functional networks reported by Bickart et al. (2012) and Touroutoglou et al. (2015) are most likely not exclusively related to emotional processing but rather serve a more general purpose. As the authors of both studies (Bickart et al., 2012; Touroutoglou et al., 2015) point out, their reported networks are highly similar to the salience network. The salience network is an intrinsic large-scale network constituted by the anterior insula, the anterior cingulate cortex (ACC), the amygdala, the ventral striatum and the ventral tegmental area (Seeley et al., 2007). In essence, it is involved in the detection of relevant stimuli from the external environment as well as from one's own bodily and cognitive state in order to guide one's perception, cognition and behaviour towards a state of homeostasis (Menon, 2015; Menon & Uddin, 2010; Seeley et al., 2007). This modulatory influence of the salience network on other brain regions can be observed exemplarily for the amygdala: Feedback loops of the amygdala have been described that allow a modulatory influence of the amygdala on early visual processing when confronted with salient stimuli (Furl, Henson, Friston, & Calder, 2013; Vuilleumier, 2015). Given the tremendous relevance of social signals for our own needs and goals, it is little surprising that the regions of the salience network have already been implicated in social cognition (Kennedy & Adolphs, 2012). Finding a loved-one in distress is a highly relevant stimulus, requires swift and adequate perception of emotional signals and likely evokes a vicarious emotional state in one self – thus combining salience detection, emotion perception and empathy in an instant.

When adopting a network perspective on the neural base of social cognition, it becomes apparent that the frequent co-occurrence of processes such as emotion perception and empathy is reflected by their overlapping brain networks. The efficiency of socio-cognitive processes is thus not dependent on the integrity of single brain regions, but on the conjoint activity of large-scale functional networks (Pessoa & McMenamin, 2017). Still, the network perspective can be taken another step further by not only analysing brain functions but also incorporate bodily functions and their role in social cognition. Physiological adaptations complement and interact with central nervous processes, and only the continuous dynamic interaction of body and brain enables us to engage with the environment (Critchley et al., 2013). This crucial role of bodily processes in social cognition is addressed in the following section.

2.3 The role of the autonomic nervous system in social cognition

A comprehensive understanding of human social cognition can only be achieved by incorporating an evolutionary perspective. In order to thrive and survive in an increasingly complex social environment, it was necessary to develop mechanisms which allow us to respond to situational demands in a way that best fits our own needs and goals (Bradley, Sabatinelli, & Lang, 2014; Smith, Thayer, Khalsa, & Lane, 2017). To accomplish accordance between opportunities and challenges rising from the environment on the one hand but also one's current needs, future expectations and past experiences, continuous adaptations of mental and bodily states emerge from the dynamic interplay of the central (CNS) and autonomic nervous systems (ANS; Critchley & Harrison, 2013; Levenson, 2014; Thayer & Lane, 2000).

In the following section, the functional principles of the ANS will be presented. The heart has frequently been studied in emotional processing (Kreibig, 2010) and offers the possibility to record dynamic psychophysiological adaptations on different time scales (Levenson, 2014), which provides the basis for the second empirical study of this thesis. Thus, the focus will be on the regulatory influence of the ANS on cardiac activity. Subsequently, the core network of brain regions involved in the interplay of bodily and mental processes will be introduced. Finally, the implications of the ongoing interplay of CNS and ANS for social cognition will be discussed.

2.3.1 Structure and function of the autonomic nervous system

The ANS consists of three subdivisions: the sympathetic nervous system (SNS), the parasympathetic nervous system (PNS) and the enteric nervous system (ENS). The ENS serves

the regulation of gastrointestinal processes and is largely independent from central nervous processes (Jänig, 2010); thus, it will not be covered further in this thesis.

With exception of functions controlled by the ENS, adaptive physiological changes are the result of the coordinated activity of the SNS and the PNS (Appelhans & Luecken, 2006). Their modulating influence on bodily functions can broadly be divided into the four divisions regulation, activation, coordination and communication (Levenson, 2014). By activation of the SNS and PNS, (i) the bodily milieu is regulated in order to maximize functioning and minimize damage, (ii) bodily resources are allocated to match the situational demand, (iii) a bidirectional flow of information between CNS and ANS is established, and (iv) visible changes in appearance are produced that can be perceived by conspecifics (Levenson, 2014).

The dynamic interplay of ANS and CNS enables the integration of bodily signals into the CNS but also open the possibility of top-down regulatory control of the CNS on ANS activity (Critchley et al., 2013; Jänig, 2010). Most organs of the human body are innervated by both branches of the ANS, whereby a stimulating effect is commonly ascribed to the SNS while activity of the PNS is associated with inhibitory influence that leads to a state of relaxation and recreation (Appelhans & Luecken, 2006; Jänig, 2010). Although SNS and PNS are often described as antagonists, their functions are better understood as complementary systems (Jänig, 2010). This can be observed at the level of the heart, where the orchestrated changes in SNS and PNS activity give rise to dynamic adaptations in cardiac functions (Shaffer, McCraty, & Zerr, 2014). Therefore, cardiac activity offers the possibility to measure the combined influence of the ANS and PNS with non-invasive methods and exhibits far-reaching influence on the whole body (Palma & Benarroch, 2014; Task Force of the European Society of Cardiology, 1996). For these advantages, analyses of heart rate were chosen as methodological approach in this thesis and thus determine the scope of the following sections.

2.3.2 Neural control of the heart

The two subdivisions of the ANS differ considerably in structure and function, which translates to differences in their potential to influence bodily functions (Levenson, 2014). For brevity, the following description is limited to the innervation of the heart.

The heart is regulated by the combined influence of the SNS and PNS on the pacemaker cells of the heart (Huppelsberg & Walter, 2013; Shaffer et al., 2014; a detailed description of cardiac functions and measures of heart rate is provided in section 3.2). Sympathetic influence on the heart is based on the release of norepinephrine, which leads to an increase in heart rate that peaks after four to five seconds and slowly returns to baseline within 20 seconds. In

contrast, parasympathetic activation via acetylcholine allows a modulatory influence on the heart on a beat-to-beat base with peak influence after 0.5 seconds and recovery within one second (Palma & Benarroch, 2014). At rest, the heart is under tonic parasympathetic control, which results in a resting heart rate that is lower than the intrinsic firing rate of the heart's main pacemaker cells (Shaffer et al., 2014). Because the parasympathetic influence on the heart is transmitted by the vagus nerve, this parasympathetic control is often referred to as vagal dominance (Thayer, Hansen, Saus-Rose, & Johnsen, 2009) or vagal tone (Task Force of the European Society of Cardiology, 1996) If necessary, this vagal dominance can be withdrawn within one heart cycle (Shaffer et al., 2014; Task Force of the European Society of Cardiology, 1996).

In absence of any modulatory influence of the SNS and PNS, the heart's inherent pacemaker nodes induce a highly invariant heart rate (Huppelsberg & Walter, 2013). Due to the different temporal dynamics of the SNS and PNS, their combined activity can induce any combination of quick (i.e. parasympathetic) as well as long-lasting (i.e. sympathetic) modulation of the heart rate (Levenson, 2014). This interplay of SNS and PNS also gives rise to changes in the time intervals between adjacent heartbeats, which is defined as heart rate variability (HRV; Task Force of the European Society of Cardiology, 1996). Various indices of HRV that capture parasympathetic or sympathetic contributions to variability in one's heart rhythm can be derived from heart rate recordings (Task Force of the European Society of Cardiology, 1996). These HRV indices reflect the efficiency of the cardiovascular system to adapt to internal and external demands on different time scales (Appelhans & Luecken, 2006; Thayer et al., 2009).

2.3.3 Interplay of central and autonomic nervous systems

The regulatory influence of the SNS and PNS on the heart largely depends on the integration of one's own physiological state as well as current goals and needs in the context of environmental opportunities and challenges (Appelhans & Luecken, 2006; Critchley & Harrison, 2013). To accomplish the integration of this wealth of information, the ANS interacts with a network of brain regions that is involved in the continuous perception and appraisal of bodily and as well as sensory information and subsequent top-down control of mental and physiological processes (Smith et al., 2017; Thayer et al., 2009). This network was described by Benarroch (1993) as the central autonomic network (CAN), which initially included the prefrontal cortex, insula, amygdala, hypothalamus, peraqueductal gray matter, parabrachial nucleus (PB), nucleus of the tractus solitarious (NTS) and the ventrolateral medulla. It was later

extended to further include the cingulate cortex (Thayer & Lane, 2000). In their Neurovisceral Integration Model, Thayer and Lane (2009) outline the pathways by which the SNS and PNS can influence the heart rate[2]. Based on contemporary findings of neuroimaging and physiological recordings, they provide a theoretical framework that describes the afferent and efferent processes that give rise to the interplay between CNS and ANS (Thayer & Lane, 2009). The interconnection of the CAN and the two autonomic branches is displayed in figure 4.

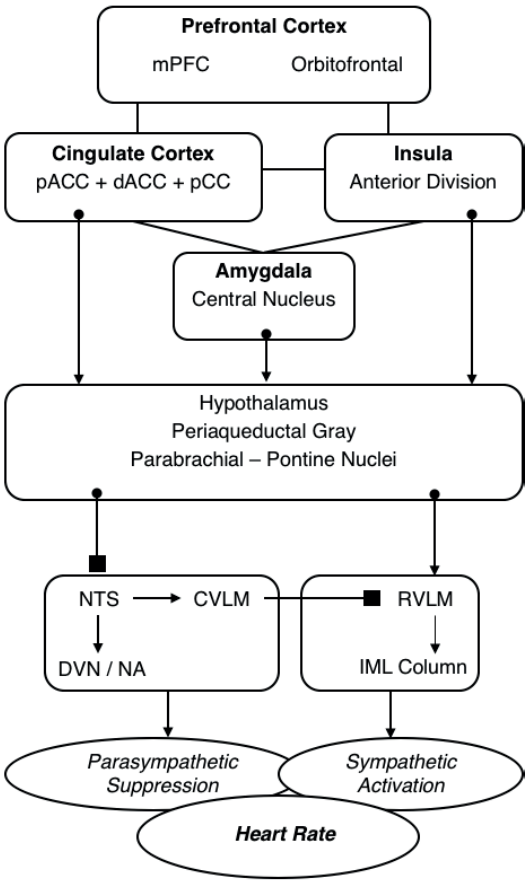

Figure 4. A schematic diagram of the pathways which enable top-down control of the central autonomic network (CAN) on the heart rate. Excitatory effects of connections to brainstem areas are indicated by arrows, inhibitory effects of connections are indicated by squares. Figure adapted from Thayer & Lane (2009).

[2] A competing perspective on the role of the ANS in social behaviour was brought forward by Porges in the Polyvagal Theory (Porges, 1995). Since core assumptions of this theory do not rely on empirical evidence and have partly been rejected by current research (Grossman & Taylor, 2007; Laborde, Mosley, & Thayer, 2017), the polyvagal theory will not be discussed further in this thesis.

A core structure of the CAN is the amygdala, which plays a central role in the rapid assessment of valence and salience of sensory input in order to appraise environmental cues regarding threat, safety and relevance for one's current needs (Adolphs, 2008; Janak & Tye, 2015; Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012). As described by Thayer and Lane (2009), activity of the amygdala can lead to an increase in heart rate by three routes that involve either increased sympathetic or reduced parasympathetic activity. First, activity of the amygdala decreases the inhibitory influence of neurons in the caudal ventrolateral medulla (CVLM) on tonically active sympathoexcitatory neurons in the rostral ventrolateral medulla (RVLM). In turn, stronger activation of the RVLM leads to a disinhibition of neurons in the interomediolateral cell column (IML; Thayer and Lane, 2009). The IML is the primary site of cardiac preganglionic sympathetic neurons, thus reduced inhibition of IML neurons results in increased sympathetic outflow and finally in an increase in heart rate (Palma & Benarroch, 2014). Secondly, the amygdala has the potential to directly activate the sympathoexcitatory neurons of the RVLM (Thayer and Lane, 2009). Thirdly, amygdala activation leads to an inhibition of the NTS and subsequently an inhibition of the Nucleus Ambiguus (NA) from which the vagal nerve originates, causing an increase in heart rate (Thayer and Lane, 2009).

In addition to the appraisal of environmental cues, visceral information regarding the bodily state such as current heart rate, blood pressure, pulmonary functions, satiety and thirst need to be incorporated in order to adequately regulate autonomic functions. These visceral signals reach the brain via ascending nerves that terminate in the NTS (Palma & Benarroch, 2014). The NTS is considered as the first site of convergence of visceral afferents and is involved in the initial integration of visceral information across many modalities (Critchley & Harrison, 2013). Projections from the NTS further relay these information to the hypothalamus, PB and via the thalamus to the posterior insula (Critchley & Harrison, 2013). Processing in the insula follows a posterior-anterior gradient: A primary interoceptive representation is formed in the posterior insula, is integrated with pre-processed sensory input from the cingulate cortex and the amygdala in the middle insula and is finally consciously accessible as representation of one's psychophysiological state in a specific situation in the anterior insula (Menon, 2015; Palma & Benarroch, 2014). Based on the insula's role in the awareness of bodily and sensory information, it has been described as "interoceptive cortex" (Pessoa & McMenamin, 2017).

Regions in the mPFC and the cingulate cortex, especially its anterior parts (anterior cingulate cortex, ACC), are the primary instances of the CAN that are implicated in the conscious regulation of autonomic functions (Benarroch, 1993; Thayer et al., 2009). Both the amygdala and the insula maintain connections to each other but also to the mPFC and ACC

(Bernhardt & Singer, 2012; Chang, Yarkoni, Khaw, & Sanfey, 2013; Kim et al., 2011), thereby forming a network that allows the holistic appraisal of a specific internal and external situation. In essence, the ACC as part of the salience network is implicated in attentional processes and cognitive control (Medford & Critchley, 2010; Palma & Benarroch, 2014; Seeley et al., 2007). In the context of neurovisceral integration, functions of the PFC such as the construction of a context consisting of past memories, expectations on future events, evaluations of costs and needs of actions as well as emotional appraisal (Bzdok et al., 2013; Stuss, 2011) are essential to guide top-down influences of the CAN on ANS activity (Smith et al., 2017).

While it is possible to delineate the sympathetic or parasympathetic influence at the level of the end organs (Jänig, 2010), the specific effect of activity of a brain hemisphere or region on the two branches is less clear. Hemispheric effects can be studied during transient inactivation of one hemisphere, that can be achieved by injection of agents such as sodium amobarbital (Wada & Rasmussen, 1960). Heart rate recordings during such injections showed an initial increase in heart rate with subsequent deceleration for both hemispheres (Ahern et al., 2001; Jokeit, Noerpel, Herbord, & Ebner, 2000), thus dismissing general hemispheric tendencies on heart rate.

Regional effects were examined by Beissner and colleagues (2013), who subsumed current literature targeting neural correlates of sympathetic activity indicated by changes in skin conductance as well as parasympathetic activity measured by HRV. When pooling studies across sympathetic and parasympathetic measures, their meta-analysis revealed involvement of distributed brain areas in autonomic regulation that are highly consistent with the CAN already proposed by Benarroch 20 years earlier (Benarroch, 1993). However, examining neural correlates of skin conductance or HRV separately led to partly divergent brain networks (see figure 5). Parasympathetic regulation was associated with bilateral activity within the insula and the left amygdala, whereas activity of prefrontal and cingulate cortices as well as of the right anterior insula was mainly found as correlates of SNS activity (Beissner et al., 2013). The left amygdala was the only region to show similar engagement in sympathetic and parasympathetic regulation (Beissner et al., 2013), which potentially reflect its modulatory pathways proposed by Thayer et al. (2009). This left-side dominance of the amygdala in autonomic regulation is supported by findings from Thayer et al. (2012). For the right amygdala, a significant correlation was found with parasympathetic activity during affective but not cognitive or somatosensory experiments (Beissner et al., 2013). The bilateral involvement of the amygdala in autonomic regulation is in line with previous findings of

Critchley et al. (2005) who report that during the perception of facial emotional expressions, the acceleration in heart rate is linked to activity in both amygdalae.

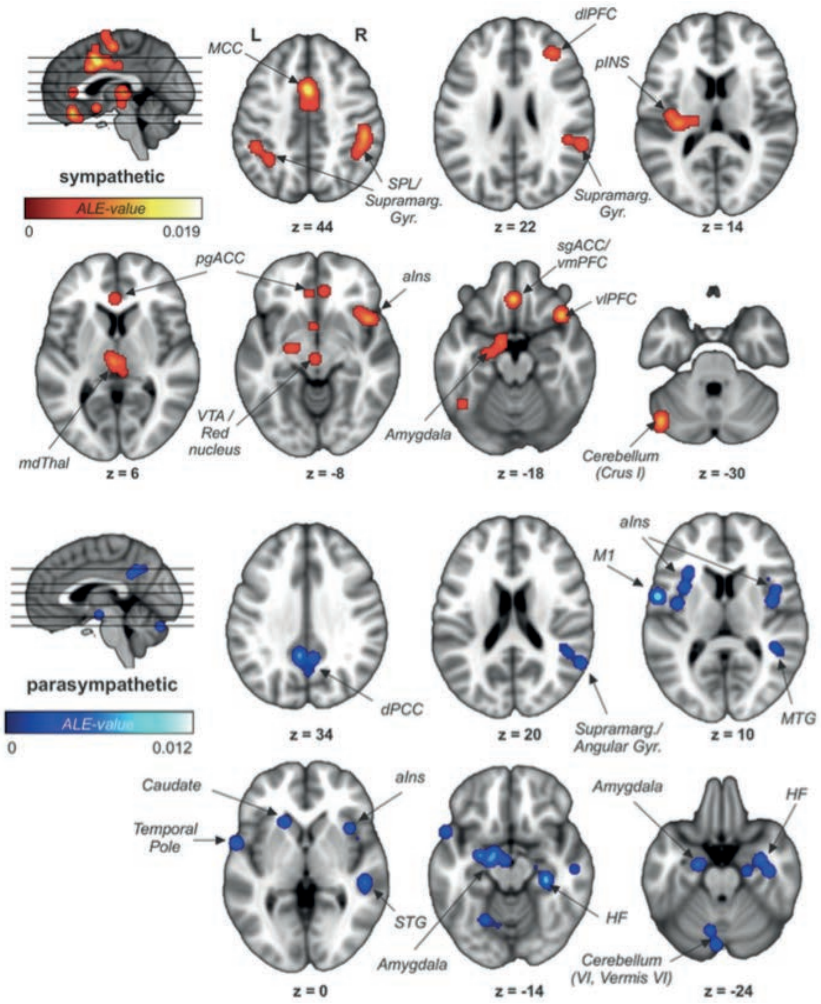

Figure 5. Brain areas associated with parasympathetic and sympathetic regulation in the meta-analysis of Beisser et al. (2013). Figure adapted from Beissner et al. (2013). aIns, anterior insula; dlPFC, dorsolateral prefrontal cortex; dPCC, dorsal posterior cingulate cortex; HF, hippocampal formation; M1, primary motor cortex; MCC, medial cingulate cortex; mdThal, mediodorsal thalamus; MTG, medial temporal gyrus; pgACC, pregenual anterior cingulate cortex; pINS, posterior insula; sgACC, subgenual anterior cingulate cortex; SPL, superior parietal lobe; STG, superior temporal gyrus; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex; L, left; R, right.

The question of lateralisation has also frequently been posed for the insular cortex (Palma & Benarroch, 2014). Based on lesion studies (e.g. Oppenheimer, Kedem, & Martin, 1996) and results from stimulation of the insular cortices by use of intracranial electrodes (Oppenheimer, Gelb, Girvin, & Hachinski, 1992), previous studies often proclaimed an oversimplified model of left parasympathetic and right sympathetic regulatory influences of the insula on the heart (Palma & Benarroch, 2014). However, effects of insular stimulation could not be replicated consistently (Stephani, Fernandez-Baca Vaca, Maciunas, Koubeissi, & Lüders, 2011). In the meta-analysis of Beissner et al. (2013), activity of the insular cortex showed correlations with SNS and PNS activity, but the anterior/posterior as well as left/right localisation differed between the two branches: SNS activity could be linked to left posterior and right anterior insula activity, whereas PNS activity was correlated with bilateral activity of the anterior insular cortices. These findings dismiss the previously held belief of a left/right dichotomy on behalf of a more complex role of the insula with different regulatory properties of its subdivisions in both hemispheres.

In conclusion, studies combining physiological recordings and neuroimaging provide broad evidence for the autonomic regulatory capacity of the CAN and consequentially the dynamic interplay of ANS and CNS in a shared effort to coordinate bodily and mental states in order to attain goals and react to environmental challenges. In the following section, it will be discussed how these processes of neurovisceral integration set boundaries for and find expression in social cognition.

2.3.4 Importance of neurovisceral integration for social cognition

The key involvement of bodily adaptations in emotional processing enables many ways to approach social cognition from a psychophysiological perspective. For the current thesis, two main aspects of neurovisceral integration are important. First, measures of HRV are currently discussed as a potential trait-like indicator of autonomic and emotional adaptability and flexibility that ultimately should reflect the efficiency of the interplay between ANS and CNS (Appelhans & Luecken, 2006; Thayer et al., 2012). Secondly, bodily adaptations in a specific situation can serve as a window into the psychophysiological component of emotional experiences (Kreibig, 2010). These emotional experiences may arise genuinely from the individual itself as response to the environment (Levenson, 2014) or can be evoked by the empathetic sharing of an affective state of another person (Critchley & Harrison, 2013). Major findings covering these two pathways towards neurovisceral integration in social cognition will

be summarized next to serve as empirical foundation for the following empirical part of this thesis.

In the clinical context, HRV has been recognized as an indicator of high relevance for health-related outcomes and mortality (Appelhans & Luecken, 2006; Thayer & Lane, 2007). While the precise mechanism is not yet understood, it is assumed that low HRV partly results from autonomic dysregulation based on misjudged signals of threat and safety in the external environment and consequentially maladaptation of mental and bodily states (Kemp, Koenig, & Thayer, 2017; Thayer et al., 2012). In the framework of the Neurovisceral Integration Model, HRV expresses the modulatory capacity of the CAN in order to induce situation-specific psychophysiological adaptations (Thayer & Lane, 2009). Based on the versatile roles of many structures of the CAN in affective and cognitive regulatory processes as well as their potential to give rise to physiological adaptations, HRV is interpreted as a global indicator of emotional and autonomic flexibility (Appelhans & Luecken, 2006; Thayer & Lane, 2000). Thus, HRV is assumed to reflect the integrity of functions of the CAN that support goal-directed cognition and behaviour (Thayer et al., 2009). A large reduction of HRV would indicate a lack of modulatory influence of the CNS on cardiac functions (Jänig, 2010).

Research on the behavioural correlates of HRV led to diverse results. Larger HRV has been found in individuals with more efficient emotion regulation strategies (Geisler & Kubiak, 2009; Williams et al., 2015), lesser tendencies for rumination (Williams et al., 2015) as well as more prosocial behaviour (Beffara, Bret, Vermeulen, & Mermillod, 2016). In contrast, lower HRV was been related to instability of positive affect during daily living (Koval et al., 2013), which supports the link between emotion regulation and HRV (Appelhans & Luecken, 2006). Regarding the perception of social signals, Quintana et al. (2012) reported that individuals with higher HRV are more successful in the inference of affective and mental states of others based on photographs of their eye region. Park and colleagues point out that high HRV is associated with more efficient perceptive and attentional processing of emotional facial expressions (Park & Thayer, 2014). Therefore, many studies are consistent with the proclaimed interpretation of HRV as indicator of central nervous regulatory capacities and autonomic flexibility in social situations. However, controversial findings challenge this interpretation (Muhtadie, Koslov, Akinola, & Mendes, 2015; Tracy & Giummarra, 2017) and call for further empirical studies to clarify the behavioural implications of HRV.

While the relatively young theoretical framework on the behavioural relevance of HRV (Appelhans & Luecken, 2006; Benarroch, 1993; Porges, 1995) emerged alongside with methodological advances that allowed insight into cardiac as well as brain functions, alterations

of physiological processes in the course of emotions have been recognized since the early work of Darwin (1872). In the time since, scientists adopted almost diametrical positions in their attempts to clarify the role of physiological changes in emotional processing. For a start, James and Lange held the perspective that bodily sensations as responses to emotive stimuli are the building blocks for emotions, which result from the perception of said bodily changes (Lange & James, 1922). In reply, Cannon criticized that emotions cannot possibly stem from the body for bodily changes are too slow and not distinct enough to produce the variety of emotional experiences. Instead, Cannon described the CNS as source of emotions (Cannon, 1927).

In 1962, Schachter and Singer presented a highly influential series of experiments in which they could demonstrate that subjective experiences of emotions depend on the combination of physiological arousal but also the integration of contextual information that allows the attribution of one's arousal to a particular emotion (Schachter & Singer, 1962). In line with this notion, numerous theories on the emergence of emotions have been brought into the discussion (Gendron & Feldman Barrett, 2009; Lindquist et al., 2013). It appears that the initial question whether the body or the brain gives rise to emotions has been abandoned for more integrative frameworks that highlight the continuous interaction of bodily and mental processes (Barrett, 2016; Levenson, 2014; Smith et al., 2017). Despite the conceptual differences among research groups, there is no doubt that emotions are multidimensional, psychophysiological constructs that coordinate mental and bodily states towards the fulfilment of needs and goals in situations relevant to the individual (Schirmer & Adolphs, 2017). In healthy individuals, adaptations of one's bodily state during emotions are assumed to support adaptive behaviour such as the increase in muscle tone and heart rate when in anger (Quigley & Barrett, 2014). As part of this physiological adaptations, emotions are accompanied by visible signals such as changes in the coloration of the skin, facial expression, body posture, pupil dilation or sweating (Critchley et al., 2013; Levenson, 2014). These signals can be perceived by others and facilitate communication and social interactions (de Vignemont & Singer, 2006).

Although no consensus on the origin of emotions has been achieved so far, this should not prevent research on facets of emotions. At least, the objection of Cannon (1927) regarding the ANS' lacking capability for quick and patterned activity could be refuted. Discoveries on the principles of action of the SNS and PNS revealed that due to their reliance on disparate neurotransmitter system and consequentially different time scales of influence, the ANS is capable of highly distinct patterns of activity across many organs (Levenson, 2014; Palma & Benarroch, 2014). This opens up many questions regarding the physiological facet of emotions.

Albeit the structure and functions of the ANS enable fine-tuned alterations in physiology, it is not yet clear whether specific emotions rely on a unique pattern of ANS activity, or if all emotions share similarities in their physiological substrate (Levenson, 2014).

Meta-analytic findings on studies using various paradigms to evoke emotions and record the corresponding physiological adaptations fall between these two extreme positions (Cacioppo et al., 2000; Kreibig, 2010; Stemmler, 2004). In the latest and most comprehensive meta-analyses on this matter so far, Kreibig (2010) presents tendencies of physiological adjustments during emotion. The most common paradigms to evoke emotions are film clips, personalized recall of emotional experiences, real-life manipulation (e.g. fear of electric shocks in an experiment), emotive pictures or imagery. Across these approaches, the following tendencies could be observed: induction of anger and fear was accompanied by an increase in heart rate and decease in HRV, sadness was associated with decreases in heart rate and HRV, an increase in heart rate and HRV was present in joy, and mixed findings of accelerated and decelerated heart rate were found for disgust depending on whether the stimulus contained contamination (acceleration) or bodily mutilation (deceleration; Kreibig, 2010). Findings for more complex emotions such as amusement or pride were less distinct (Kreibig, 2010). These results already point out that solely based on measures of heart rate or HRV, it is not possible to distinguish specific emotions. Additionally, the interaction between characteristics of the emotive stimuli and the observer can lead to different reactions. While a distant threat likely induces a deceleration of heart rate in the course of an orienting response (Bradley, Codispoti, Cuthbert, & Lang, 2001; Bradley et al., 2014), heart rate increases with proximity of the threat in order to prepare behavioural responses to the imminent danger (Bradley et al., 2014; Kreibig, 2010).

A common pitfall in paradigms that aim at evoking emotions is the uncertainty to what degree a stimulus actually induces an emotion, and if the desired emotion is evoked or rather an alternative one (Levenson, 2014). Disparate emotional responses to identical stimuli could explain why studies on the similarity of heart rate responses to emotive stimuli reported low to moderate correlation between psychophysiological adaptations of participants (Golland, Arzouan, & Levit-Binnun, 2015; Golland, Keissar, & Levit-Binnun, 2014). To address this question of possible diversity, innovative paradigms and methodological approaches are necessary to discern psychophysiological patterns during emotional experiences (further information is provided in the methodological background section 3.2.3). Nevertheless, it can be concluded that paradigms that aimed to evoke emotions have provided evidence for reliable

autonomic adaptations in emotional experiences that can be grouped into emotion-specific patterns to some degree (Kreibig, 2010).

Psychophysiological adaptations are not only part of genuine emotions that one experiences first-hand, but also constitute an important component of empathy (Singer & Lamm, 2009). Due to the shared neural origin of genuine and vicarious emotions, the observation of an affective state in another person should give rise to a similar psychophysiological state in oneself including bodily adaptation (Critchley et al., 2013; Lamm et al., 2017). Therefore, observing the fear of another person would be associated with an acceleration of one's own heart rate. Although empathy is a key motivator in social behaviour (de Vignemont & Singer, 2006), this line of research has received little attention so far. First studies indicate that higher empathy is indeed linked to larger changes in heart rate during the perception of social situations (Oliveira-Silva & Gonçalves, 2011; Truzzi, Setoh, Shinohara, & Esposito, 2016). Measures of HRV have yielded mixed results in the context of empathy. While the inference of internal states of others was found to be more efficient in individuals with larger HRV (Quintana et al., 2012), results for empathetic concern are ambiguous (Tracy & Giummarra, 2017).

To sum up, the CAN as main central nervous regulatory instance and the ANS form a regulatory system with a bidirectional flow of information (Benarroch, 1993) that serves the adaptation of bodily and mental states in order to cope with challenges posed by the environment and the internal milieu (Thayer & Lane, 2009). Emotions arise from the appraisal of a specific situation, one's goals and needs but also the physiological state of the body and coordinate cognition and behaviour (Cacioppo et al., 2000). While physiological adaptations are a core component of emotions, their underlying patterns of physiological activity are not yet fully understood. This question can be addressed by analyses of heart rate. These analyses provide the opportunity to investigate the modulatory influence of the CAN on the heart via SNS and PNS activity, which results in changes in heart rate and HRV (Critchley et al., 2013). However, innovative approaches are needed to gain a better understanding of the psychophysiological facet of emotions. Such approaches could involve the investigation of HRV as marker of autonomic flexibility (Appelhans & Luecken, 2006) as well as analyses of heart rate trajectories during emotional experiences. With regard to the interconnectedness of processes in social cognition, psychophysiological adaptations during emotions likely also play a major role in more complex socio-cognitive functions like empathy, which is assumed to draw on the sharing of emotional states (de Waal & Preston, 2017). The second empirical study of this thesis falls into this area of research and focusses on the interindividual diversity of heart

rate responses to emotive stimuli. Furthermore, the role of empathy in emotionally driven changes of heart rate is examined.

2.4 Social cognition in mesial temporal lobe epilepsy

Previous sections have outlined that social cognition comprises a range of basic sensory and advanced functions that rely not only on overlapping large-scale brain networks, but also on the adaptive interplay of central nervous and autonomic processes. The extensive neural substrate of social cognition enables quick and efficient social interactions, yet it is susceptible to the detrimental influences of functional or structural brain lesions (Pessoa & McMenamin, 2017). This vulnerability is reflected in the frequent occurrence of socio-cognitive deficits in neurological and psychiatric diseases (Cotter et al., 2018; Milders et al., 2003). Individuals with epilepsy are in the focus of the first empirical study of this thesis, for they frequently feature coinciding alterations in neural networks and socio-cognitive functions. In the following sections, a general introduction to epilepsy (2.4.1) is followed by an outline of current findings in social cognition (2.4.2) and neural networks (2.4.3) in temporal lobe epilepsy.

2.4.1 Definition of epilepsy and mesial temporal lobe epilepsy

Epilepsy is one of the most frequent neurological diseases with a prevalence of approximately 0.5 to 1% in the population and largest incidence rates in childhood as well as above the age of 60 years (Forsgren, Beghi, Oun, & Sillanpää, 2005; Sander, 2003). The International League Against Epilepsy defines epilepsy as a neurological disease of the brain that is characterized by an enduring predisposition to generate epileptic seizures (Fisher et al., 2005, 2014). For the diagnosis of epilepsy, at least two unprovoked seizures that are more than 24 h apart or one unprovoked seizure with a probability of over 60% for further seizures need to occur (Fisher et al., 2005, 2014). Seizures are signs or symptoms caused by abnormal excessive or synchronized neuronal activity and are usually self-limited in time (Fisher et al., 2005). Based on the revised classification manual, they can be broadly classified into two subcategories (Berg et al., 2010; Fisher et al., 2017): Focal seizures originate within a network that is limited to one hemisphere, whereas generalized seizures rapidly emerge from bilaterally distributed brain networks. Focal seizures can further be divided into seizures with preserved or impaired awareness. Seizures with generalized onset can be either characterized by motoric components (e.g. tonic-clonic seizures) but can also occur without motoric signs (e.g. absence seizure). In approximately two thirds of all individuals with epilepsy, seizure freedom is achieved by continuous treatment with antiepileptic drugs (AED; Bernhardt, Hong, Bernasconi,

& Bernasconi, 2013; Engel, 2001). For those who do not benefit from AED treatment, surgical resection of the epileptogenic brain area offers an additional chance for complete or at least improved seizure control in approximately two thirds of the cases (Spencer & Huh, 2008; Téllez-Zenteno, Dhar, & Wiebe, 2005).

In the adult population, mesial temporal lobe epilepsy (MTLE) is the most common and also most uniform type of focal epilepsy (Téllez-Zenteno & Hernández-Ronquillo, 2012). It is characterized by recurrent seizures originating from the hippocampal formation, which in many cases shows structural and functional alterations in the course of hippocampal sclerosis (Engel, 2001; Thom, 2014). Many people with MTLE have a childhood history of febrile seizures or head injuries within the first four to five years in their lives, yet the mechanisms that link these injuries to hippocampal sclerosis are not yet understood (Scott, 2014; Thom, 2014). While seizures in MTLE with hippocampal sclerosis are initially often well controlled with AEDs, seizures tend to re-occur in early adulthood in an often drug-resistant form (Engel, 2001; Téllez-Zenteno & Hernández-Ronquillo, 2012). In these cases of MTLE, resective surgery of the hippocampal formation and possibly further parts of the temporal lobe is ultimately the treatment of choice (Engel, 2001).

In MTLE, but also in other types of epilepsy, seizures are often not the sole health complaint of affected individuals. Psychiatric comorbidities such as depression, adjustment disorders and anxiety disorders are a frequent feature of epilepsy (Lin, Mula, & Hermann, 2012; Quintas et al., 2012) and contribute to the social stigma that is experienced by many people with epilepsy in their daily lives (Jacoby, Snape, & Baker, 2005). In addition, the underlying brain lesions that give rise to seizures are furthermore causing neuropsychological deficits in the cognitive domains that rely on the afflicted brain regions (Bora & Meletti, 2016; Stretton et al., 2012). The sum of cognitive, psychiatric and social comorbidities as well as recurrent seizures and their treatment have the potential to impair quality of life in people with epilepsy significantly (Steiger & Jokeit, 2017; Szemere & Jokeit, 2015). This highlights the necessity of research on the alterations of brain activity and connectivity in people with epilepsy in order to gain a better understanding of their brain functions and behaviour. In this thesis, the focus lies on individuals with MTLE since their type of epilepsy is of high prevalence (Téllez-Zenteno & Hernández-Ronquillo, 2012) and offers a homogeneous clinical presentation (Engel, 2001).

2.4.2 Socio-cognitive deficits in mesial temporal lobe epilepsy

Aside from neuropsychological deficits in major cognitive domains such as memory, language, attention and executive functions (Elger, Helmstaedter, & Kurthen, 2004; Jokeit &

Steiger, 2016; Stretton & Thompson, 2012), socio-cognitive impairments are a common finding in many individuals with MTLE. These deficits are already apparent at the stage of emotion perception. In a meta-analysis on the most frequently tested domain of facial emotion recognition, Bora and Meletti (2016) demonstrated significant difficulties of individuals with MTLE in the recognition of all basic emotions in faces. On a cross-sectional level, these deficits were found in pre- and postsurgical phases of treatment and were most pronounced in the recognition of fearful facial expressions (Bora & Meletti, 2016). When comparing people with MTLE to healthy people, their proficiency in facial emotion recognition at the group level is approximately 20% lower (Monti & Meletti, 2015). However, only 30-50% of people with MTLE show substantial deficits on the individual level (Bonora et al., 2011; Meletti et al., 2009), which suggests that clinical variables can lead to large interindividual differences. Duration of epilepsy as well as age at epilepsy onset have been discussed as major contributing factors (Monti & Meletti, 2015), for deficits in emotion recognition have already been found in children with temporal lobe epilepsy (Golouboff et al., 2008). This could indicate an early disruption in the maturation of processes of emotion perception. In addition to the facial presentation of emotions, deficits in people with MTLE could also be shown in experiments applying voices (Broicher, Kuchukhidze, et al., 2012) or emotionally charged music (Gosselin, Peretz, Hasboun, Baulac, & Samson, 2011) of comparable effect sizes. Deficits in different modalities coincide in some individuals, but unimodal impairments are frequently observed as well (Bonora et al., 2011; Fowler et al., 2006).

Socio-cognitive impairments have not only been reported for the recognition of emotions, but further extend to ToM functions as well. This was shown by Schacher and colleagues (Schacher, Winkler, et al., 2006) who report worse performance in the faux-pas test for people with MTLE in pre- and postoperative stages compared to healthy individuals. Following studies supported (Giovagnoli, Parente, Villani, Franceschetti, & Spreafico, 2013) and extended these findings to further paradigms of ToM such as false belief tasks, cartoon ToM stories or the inference of intentions from moving shapes (Broicher, Kuchukhidze, et al., 2012; Wang et al., 2015). Assessing empathy in MTLE has proven to be difficult, for many people with MTLE are not adequately aware of their neuropsychological deficits (Giovagnoli, 2013). Additionally, empathy is frequently captured by self-report scales, which tend to show little correspondence to behavioural variables (Broicher, Kuchukhidze, et al., 2012).

Regarding the impact of socio-cognitive deficits on the daily life with MTLE, findings are mixed so far. In the study of Broicher and Kuchukhidze et al. (2012), socio-cognitive functions were assessed with a comprehensive test battery, yet no correlation between any of

the measures of emotion recognition and ToM and self-report scales on depression, quality of life and empathy could be observed. In contrast to this study, significant associations between ToM performance and quality of life (Giovagnoli et al., 2013; Wang et al., 2015) as well as social engagement, communication difficulties and employment status (Wang et al., 2015) have been reported.

In sum, impairments in multiple domains of social cognition are a frequent feature of MTLE in many – but not all – affected individuals. The potential impact of these deficits on the social life of people with MTLE is discussed in the theoretical study of this thesis. However, many of these socio-deficits are not specific for MTLE but can be found in different types of epilepsy such as epilepsy originating from the frontal lobes as well (Stewart, Catroppa, & Lah, 2016). This likely reflects the extensive neural substrate of social cognition and consequentially the vulnerability of social cognition to lesions within supporting large-scale networks. To address the neural level of social cognition in MTLE, current findings on alterations in brain activity and connectivity are presented next.

2.4.3 Functional brain alterations in mesial temporal lobe epilepsy

Functional and structural alterations of the brain in MTLE extend far beyond the hippocampus and the amygdala (Caciagli, Bernhardt, Hong, Bernasconi, & Bernasconi, 2014; Keller et al., 2015). Widespread functional changes throughout the brain have been observed by use of fMRI (Caciagli et al., 2014) but also other techniques such as position emission tomography (Jokeit et al., 1997). With regard to the first empirical study of this thesis, an overview on functional activity and connectivity in MRI studies in the context of emotion perception and is given next.

Neural correlates of emotion perception in people with MTLE have mostly been studied by use of pictures or film clips depicting fearful facial expressions compared to either neutral faces (e.g. Benuzzi et al., 2004) or control conditions such as dynamic landscapes (Schacher, Haemmerle, et al., 2006). So far, two general tendencies could be observed. First, the response to fearful facial expressions is more pronounced in the contralateral hemisphere than in the hemisphere of seizure onset (Ives-Deliperi, Butler, & Jokeit, 2017; Labudda, Mertens, Steinkroeger, Bien, & Woermann, 2014; Schacher, Haemmerle, et al., 2006; Toller et al., 2015)

Secondly, right-sided MTLE has been associated with more severe disruptions of the brain response to fearful facial expressions. While people with left-sided MTLE showed involvement of the right amygdala, such a recruitment of the contralateral left amygdala was not consistently observed in individuals with right-sided MTLE (Labudda et al., 2014; Toller

et al., 2015, but see Bonelli et al., 2009). The importance of functional integrity of the right amygdala was highlighted by Labudda et al. (2014), who showed that in left-sided MTLE, the degree of functional lateralization in favour of the contralateral right amygdala was correlated with post-scanning ratings of fear in the stimulus material. In right-sided MTLE, no such correlation could be observed. In addition, Toller et al. (2015) report a positive correlation between activity of the right amygdala and self-reported feelings of empathetic concern towards others across study participants with and without epilepsy. A first post-surgical study of von Åhs et al. (2014) showed that these functional alterations in response to facial emotional expressions are also present in people who underwent resection of the anterior temporal lobe including the amygdala. In comparisons to healthy participants, post-surgical participants showed decreased activation of the right STS regardless of the side of resection. However, in cases of right-sided resection, weaker activity of the fusiform gyrus and occipital face-selective areas was observed. These post-surgical findings further substantiate the key role of the amygdala in the processing of facial emotional expressions and its modulatory influence on the face processing network. In sum, these studies on the processing of fearful facial expressions in people with MTLE demonstrate that functional alterations are present within the afflicted mesial temporal lobe but also extend to distributed brain areas involved in the processing of facial expressions and faces in general.

In line with the change of paradigm in neuroimaging from single regions to brain networks, research efforts aiming at alterations of functional brain networks in MTLE have increased drastically during the last century. Ultimately, epilepsy has been characterized as a disease of brain networks instead of brain regions (Berg et al., 2010), which is reflected in the latest classification of seizures (Fisher et al., 2017). Recent findings on FC support this concept by demonstrating that the synchronization of whole-brain intrinsic functional networks is disrupted in MTLE (Caciagli et al., 2014; Pittau et al., 2014). So far, most studies in MTLE focused on the integration of the hippocampus in intrinsic networks and have shown decreased functional connectivity among the affected hippocampus and local ipsilateral (Bettus et al., 2009; Maccotta et al., 2013; Pittau, Grova, Moeller, Dubeau, & Gotman, 2012) as well as distant, especially contra-lateral brain regions (Liao et al., 2011; Pittau et al., 2012). However, increased connectivity of the hippocampus and the ipsilateral insula (Macotta et al., 2013) and thalamus (Haneef et al., 2014) has been reported as well and was attributed to their frequent functional coupling with the hippocampus during seizure propagation (Englot, Konrad, & Morgan, 2016)

In contrast to the functional decoupling of the affected mesial temporal lobe, increased FC was found within the contralateral mesial temporal lobe (Bettus et al., 2009) and for brain regions in networks that initially comprised the afflicted hippocampus (Zhang et al., 2010). This heightened connectivity has been interpreted as compensatory network re-configuration in the course of MTLE (Pittau et al., 2014). Additionally, network alterations in MTLE are linked to clinical characteristics. Change in FC of the afflicted mesial temporal lobe is associated with the duration and severity of the disease (Liao et al., 2011; Morgan, Conrad, Abou-Khalil, Rogers, & Kang, 2015; Voets et al., 2009). While network alterations are currently discussed as source of information regarding a patient's responsiveness to surgical treatment (Morgan et al., 2015; Pittau et al., 2014), network alterations prevail even in post-surgical cases that achieved seizure freedom (Maccotta et al., 2017), thus indicating a lasting effect of MTLE on the brain's intrinsic functional networks.

With regard to the focus of this thesis, alterations in the functional connections of the amygdala as key region in social perception are of special importance. Studies on the intrinsic FC of the amygdalae in MTLE consistently showed more extensive alterations in people with right-sided MTLE, in whom network alterations were present for both amygdalae, whereas predominately left-sided network alterations were observed in cases of left-sided MTLE (Doucet, Skidmore, Sharan, Sperling, & Tracy, 2013; Pittau et al., 2012). Reduced intrinsic FC of the amygdala is mainly found for the hippocampus (Bettus et al., 2009; Pittau et al., 2012) as well as cingulate and prefrontal cortices (Doucet et al., 2013; Maccotta et al., 2013; Pittau et al., 2012; but see Kemmotsu et al., 2013 for non-significant findings) and the insula (Doucet et al., 2013). These network alterations gain clinical relevance from their correlation with self-reported anxiety (Doucet et al., 2013) and depressive symptoms (Kemmotsu et al., 2013), pointing out a potential link between intrinsic network alterations and psychiatric comorbidities in MTLE. Regarding the behavioural implications of network alterations, Broicher and colleagues (Broicher, Frings, et al., 2012) demonstrated lateralized disruptions of a task-related network centred on the amygdala during the perception of dynamic fearful faces in people with left- and right-sided MTLE. Alterations of the task-related amygdala network were present in cases of left- and right-sided MTLE, but more pronounced in right-sided MTLE.

In summary, MTLE can be described as a network disease characterized by seizures originating from an epileptogenic network centred on the hippocampus. On the behavioural level, people with MTLE find themselves challenges by deficits in many cognitive domains, and deficits in socio-cognitive functions such as recognizing emotional expressions from faces pose a significant challenge to their social integration and quality of life. These frequently

observed behavioural deficits possibly stem from disruptions of the underlying neural networks. Consistently, neuroimaging studies on the neural activity related to socio-cognitive functions as well as studies on intrinsic functional networks have demonstrated functional impairment of the amygdala as key region in social cognition, yet functional disruptions further extend to large-scale brain networks. These coinciding deficits on the behavioural and neural level highlight the relevance of studies that directly target the underlying networks of social cognition in MTLE, which is the aim of the first empirical study of this dissertation.

3 Methodological background

This thesis aims to investigate neural and psychophysiological correlates of social cognition and thus adopts a multi-method-approach covering functional brain imaging as well as analyses of heart rate and HRV as measures of autonomic adaptation. In the following section 3.1, the basic principles of fMRI and its application in analyses of task-related activity and functional connectivity are summarized. In section 3.2, the biological background of heart rate and HRV as well as the computation and utilisation of corresponding measures are presented.

3.1 Functional Magnetic Resonance Imaging

Functional MRI is a powerful tool employed in neuroimaging which allows to capture dynamic metabolic changes in brain tissue and offers an in-vivo method to measure fluctuations in brain activity. Estimating neural and glial activity is made possible by the haemodynamic response that is initiated in case of increased brain activity. In order to meet the metabolic demands of the activated brain region, an oversupply of oxygenated blood is delivered to the respective region. Oxygenated and deoxygenated haemoglobin in the blood differ in their magnetic susceptibility, therefore, the haemodynamic response induces a change in the magnetic properties. These blood oxygenated level dependent (BOLD) changes lead to a difference in the signal on T2*weighted MR images and allows to differentiate between regions of different metabolic demands (Chen & Glover, 2015; Huettel, Song, & McCarthy, 2014).

Fluctuations of brain activity occur during specific tasks but also in phases of rest such as relaxation or sleep (Buckner et al., 2013). While the investigation of task-related activity provides information on which brain regions are involved in a specific cognitive process, analyses of functional connectivity (FC) offer insight into the functional coupling of brain regions. These two differential approaches are presented next.

3.1.1 Analyses of task-related activity

Analyses of task-related brain activity stem from the basic principle to evoke and compare different mental states in the subject. Based on the observed differences between the two states, it is possible to derive the relative involvement of brain areas in the evoked states. Paradigms in fMRI studies differ in many aspects such as computational strategies to compare the BOLD signal, stimulus presentation, image acquisition and image analysis (Huettel, Song & McCarty, 2014). The presentation of stimuli is central for the first empirical study of this thesis; thus, the different strategies are outlined in short.

Stimulus presentation strategies can be divided into three main strategies: block and event-related designs as well as mixed designs. In a block design, several stimuli of the same condition are presented in a row, and different blocks are presented in an alternating order. This leads to a BOLD response of high magnitude and enables the comparisons of the evoked states (e.g. task states and task-free states). In contrast, stimuli are presented separately in event-related paradigms and the individual haemodynamic response to stimuli is investigated. Mixed designs also rely on blocks of different conditions, yet stimuli are not presented continuously but as distinct events within a block (Amaro & Barker, 2006). Although the proportion of event-related studies is growing increasingly, block design fMRI is still a powerful tool with many areas of application (Huettel, Song & McCarty, 2014).

The first empirical study of this thesis relies on an analysis of task-related activity during a block design fMRI experiment to derive areas involved in the processing of dynamic fearful faces compared to dynamic landscapes. The resulting brain regions were forwarded into an analysis of FC with the aim to investigate the functional coupling of the identified relevant brain regions. Since the analysis of FC represents the core aspect of the first empirical study, the background and application of FC is subsequently presented in more detail.

3.1.2 Functional connectivity

Research on brain activity during tasks has greatly advanced our understanding of human brain functions regarding the involvement of distinct brain regions in tasks. Conceptual as well as methodological advances in the last two decades of neuroimaging have led to the shift from functional segregation to the new paradigm of functional integration (Friston, 2011). Adopting the perspective of interconnected large-scale brain networks instead of focusing on single areas offers a new access to investigate the functional architecture of the brain (van den Heuvel & Hulshoff Pol, 2010).

Interest in the functional coupling of brain regions took off after the seminal discovery of Biswal and colleagues (1995), who were the first to demonstrate that seemingly spontaneous low-frequency (< 0.1 Hz) fluctuations in the BOLD signal of the human motor cortices showed in fact highly coherent time courses of activity (see figure 6, panel A). Although participants lay still while their brain activity was recorded, a significant correlation was observed between the left and right motor cortex, yet not between motor cortices and visual areas. Notably, this correlation occurred at rest and was not triggered by an external event. This led to the assumption that this functional coupling reflects ongoing information processing within a functional neural circuit (Biswal et al., 1995). Ever since, FC was defined as the statistical

dependency among neurophysiological events in spatially distributed brain regions (Biswal et al., 1995; Friston, Frith, Liddle, & Frackowiak, 1993; Friston, 2011).

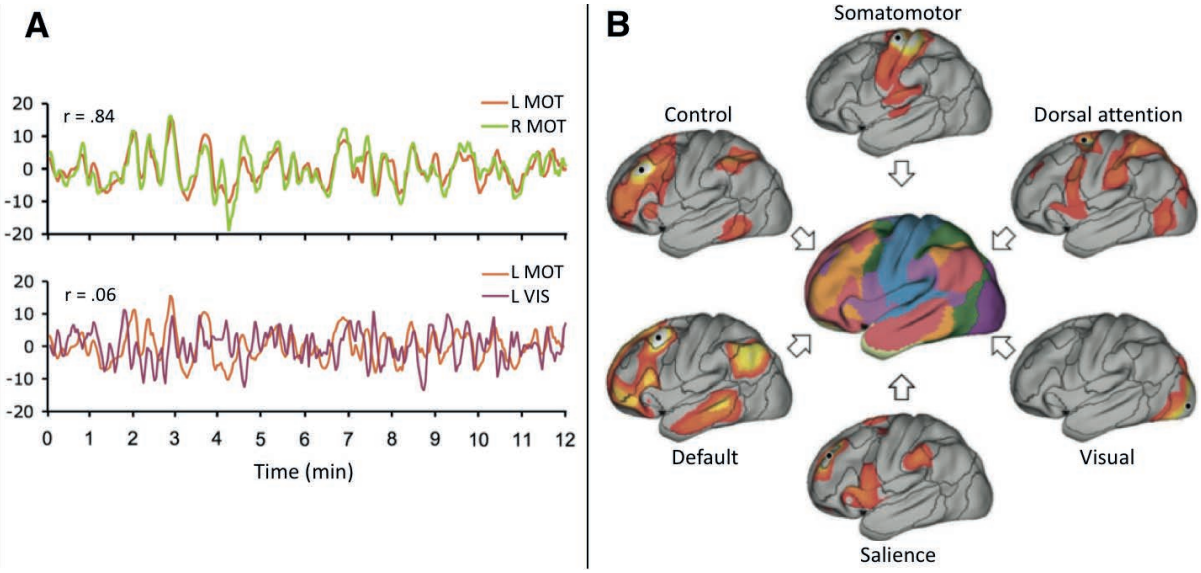

Figure 6. Origin of research on functional connectivity and currently discussed intrinsic functional networks. **A** Exemplary visualisation of Biswal and colleagues (1995) results of correlation between the BOLD time series of the left and right motor cortices but independence of BOLD time series of visual and motor cortices. Figure adapted from van Dijk et al. (2010); MOT, primary motor cortex; VIS, primary visual cortex; L, left; R, right. **B** Intrinsic functional networks observed in task-free states. Figure adapted from Buckner et al. (2013).

Building on the initial work of Biswal et al. (1995), a vast number of studies have replicated this first finding and have further uncovered numerous networks that show synchronous activity over time (Van Dijk et al., 2010). Large-scale networks overlapping with central domains of brain functioning such as language, vision, auditory processing or attention as well as the so-called default mode network (Greicius, Krasnow, Reiss, & Menon, 2003) have been documented consistently (Buckner et al., 2013; see figure 6, panel B). Early studies investigated FC while participants did not engage in any task, therefore these functional networks were termed resting state networks (Damoiseaux et al., 2006). However, this term can be misleading for two reasons. First, the existence of correlated activity in many functional networks already indicates that even in a presumed state of rest, the brain is not idle (van den Heuvel & Hulshoff Pol, 2010). Additionally, only little differences in metabolic demands of

approximately 5% were observed between task states and task-free states (Raichle & Mintun, 2006). Secondly, these networks cannot only be identified during task-free periods but are also present when cognitive tasks are performed (Gonzalez-Castillo & Bandettini, 2017). Studies comparing functional networks at rest and during task states have yielded highly overlapping results with only subtle differences in the observed functional networks (Cole, Bassett, Power, Braver, & Petersen, 2014; S. M. Smith et al., 2009). Furthermore, functional networks can also be observed under different states of consciousness such as sleep (Larson-Prior et al., 2009) or anaesthesia (Hutchison, Womelsdorf, Gati, Everling, & Menon, 2013). These findings led to the conclusion that the observed networks reflect the intrinsic functional architecture of the brain into functionally different yet interconnected networks, and therefore the term resting state was abandoned in favour of intrinsic FC within intrinsic functional networks (Buckner et al., 2013).

Various methodological approaches have been used to investigate intrinsic functional networks. While an extensive discussion of the different methods goes beyond the scope of this thesis, two main approaches are outlined briefly (see Lee, Smyser, & Shimony, 2013 and van den Heuvel & Hulshoff Pol, 2010 for an overview)[3]. Frequently, model-dependent methods have been applied to analyse FC of one specific region of interest (ROI, also called seed) with either the whole brain (seed-to-voxel FC) or previously defined target regions (e.g. ROI-to-ROI analysis). By correlating the time course of the seed with further ROIs or all brain voxels, FC of the seed area can be explored in a straightforward fashion. However, this approach depends strongly on the a-prior selection of the ROIs. Alternatively, model-free tools such as the Independent Component Analysis (ICA) allow data-driven extraction of whole-brain functional networks. In short, ICA algorithms extract statistically independent components from the fMRI data in order to explain the fluctuations of activity over time. The extracted components not only depict the different intrinsic functional networks, they can further be used to remove physiological noise from the data since noise is also subsumed in components. Despite the differences between the approaches, they yield highly comparable results and produce largely overlapping intrinsic functional networks (van den Heuvel & Hulshoff Pol, 2010).

The explanatory power of FC analyses largely depend on the appropriate handling of confounds and noise. Major sources of noise arise from the participants themselves, such as respiration, cardiac activity and head movement (Chang & Glover, 2009). Most importantly,

[3] Aside from FC, analyses of effective connectivity offer a valuable, complementary approach in the analysis of functional networks. Effective connectivity among brain regions is investigated in model-based analyses and targets the directionality of connections (Friston, 2011), yet does not find application in this thesis.

cyclical physiological processes can induce spurious correlation in the data, and need to be controlled for carefully (van Dijk et al., 2010). Various methods for corrections such as global signal regression, regression of the time courses of white matter masks and masks of cerebrospinal fluid or component based methods (e.g. CompCor, Behzadi, Restom, Liau, & Liu, 2007, see van Dijk et al., 2010 for regression-based methods) have been introduced for this matter. A further concern is the reliability of analyses of FC, which has not been determined conclusively. Studies on intra- and interindividual reliability vary from low to moderate reliability especially for long-distance connections (Honey et al., 2009) to high reliability for the strongest and positive intrinsic FC but weaker for negative intrinsic FC (Shehzad et al., 2009). Thorough de-noising of the data and appropriate choice of pre-processing steps are thus of utmost importance in order to yield reliable estimates of intrinsic functional networks (Van Dijk et al., 2010).

In sum, spontaneous fluctuations of neural activity offer a window into the intrinsic functional architecture of the brain. Analyses of intrinsic FC can be a powerful tool to gain information about the functional circuits of the brain, yet require careful pre-processing and thoughtful choice of methodological approach.

In the first empirical study of this thesis, FC was investigated among regions involved in the processing of facial emotional expression. Although fMRI data was recorded during a task involving the presentation of dynamic fearful faces and dynamic landscapes in a block design, regressing out task-related activity allowed us to investigate intrinsic FC (Gonzalez-Castillo & Bandettini, 2017). Task states exert a rather small yet not negligible influence on intrinsic functional networks (Cole et al., 2014), thus the findings of this study should only be interpreted in the context of emotional face processing. However, our approach offers an opportunity to make best use of fMRI data from patients, which are usually a scarce yet highly informative resource.

3.2 Heart rate and heart rate variability

In addition to brain imaging, analyses of heart rate and HRV complete the methodological approach towards social cognition of this thesis. Analyses of cardiac activity were selected in this thesis for they offer the possibility to study the temporal dynamics and trajectories of one's heart rate in active states (Kreibig, 2010) as well as influences of the CAN at rest expressed in HRV (Palma & Benarroch, 2014; Thayer & Lane, 2000). In the following section, fundamental principles of cardiac activity and the neural control the heart are reviewed. Subsequently, different approaches to analyse recordings of heart rate are presented.

3.2.1. Introduction to cardiac functions

The heart is an essential component of the cardio-vascular system and induces the continuous circulation of blood throughout the body by rhythmic contraction of the two atria and ventricles (Huppelsberg & Walter, 2013). Contraction of the heart muscle (i.e. the myocardium) is initiated by action potentials generated within autorhythmic cells of the heart that form so-called pacemaker nodes within the cardiac conduction system (see figure 7 panel A). The two pacemakers of the heart that are primarily responsible for the initiation of heart cycles are the sinoatrial (SA) node and the atrioventricular (AV) node (Shaffer et al., 2014). In a healthy functioning heart, the SA node is the origin of each cardiac cycle and initiates a cascade of processes by its depolarization: The electrical impulse of the SA node is relayed through the atria to the AV node within 30 ms and leads to a depolarization of the AV node. Subsequently, the signal is passed on along the Bundle of His, which splits into the left and right bundle branch with the Purkinje fibres extending over the ventricles and ultimately initiate the contraction of the myocardium (Jänig, 2010; Palma & Benarroch, 2014; Shaffer et al., 2014). The conduction of the electrical signal throughout the heart within one cardiac cycle can be recorded from the body's surface by the application of an electrocardiogram (ECG). Different components of the cardiac cycle produce distinct voltage changes (see figure 7 panel B), whereby the QRS-complex is the most prominent characteristic of the ECG signal and reflects the spread of the electric activity in the ventricles of the myocardium (Jänig, 2010).

In the absence of autonomic regulatory influences, the SA node spontaneously generates 60-100 action potentials per minute (Opthof, 2000; Shaffer et al., 2014). If the SA node fails to generate the initial electric impulse to start a cardiac cycle, the remaining components of the cardiac conduction system can substitute this function, yet on a lower firing rate. As secondary pacemaker, the AV node has an intrinsic firing rate of 40-60 depolarizations per minute, and as last instance, the Purkinje fibres can induce 20-30 heart cycles per minute (Huppelsberg & Walter, 2013). These intrinsic firing properties of the cardiac conduction system serve to uphold cardiac activity as long as possible in the case of malfunctioning pacemaker nodes. In healthy individuals, a resting heart rate of 60 to 80 beats per minute (bpm) can be observed (Huppelsberg & Walter, 2013). A heart rate below 50 bpm is defined as bradycardia (Jänig, 2010), whereas as a rule of thumb, 220 bpm minus a person's age in years determines the upper limit of one's heart rate (Ahmed et al., 2017).

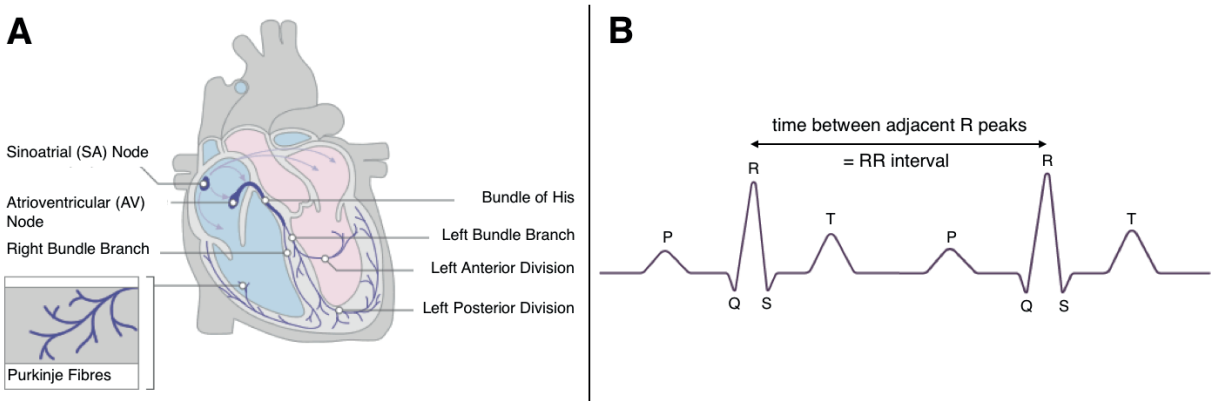

Figure 7. **A** Schematic visualisation of the cardiac conduction system consisting of the sinoatrial (AV) node, atrioventricular (AV) node, the Bundle of His with a left and right bundle branch and the Purkinje fibres. Figure adapted from The University of Nottingham (n.d.); **B** Schematic visualisation of two adjacent QRS-complex recorded by use of an electrocardiogram (ECG). The time between two adjacent R peaks defines the RR interval, which serves as the base for heart rate analyses. Figure adapted from The University of Nottingham (n.d.).

Cardiac functions are controlled by the combined influence of sympathetic and parasympathetic activity to a large extent. Increased activity of the SNS on the heart results in an increased firing rate of the SA node, faster conduction through the AV node and larger excitability of the His Bundle and Purkinje fibres. Additionally, sympathetic activity heightens the force of contraction of the myocardium and increases the speed of relaxation of cardiac muscles after contraction (Palma & Benarroch, 2014). Parasympathetic activity inhibits the activity of the SA node, decelerates conduction of the AV node and decreases the excitability of the His bundle and Purkinje fibres (Palma & Benarroch, 2014). In sum, activity of the SNS leads to an increase in heart rate and stronger contraction of the myocardium, whereas PNS activity induces an increase in heart rate. The conjoint activity thus modulates cardiac functions and can bring forth a multitude of adaptations of the cardiovascular system (Levenson, 2014) These adaptations can be measured with different approaches, which will be outlined in the next section.

3.2.2 Analyses of heart rate and heart rate variability

The starting point for every analysis of heat rate or heart rate variability is the determination of cardiac cycles from the ECG signal. Cardiac cycles are most reliably identified by the R-peak of each QRS-complex. Consequentially, the interval between two adjacent normal QRS complexes is defined as the normal-to-normal (NN) interval, sometimes also referred to as RR-interval because of its deduction from the R-peaks (Task Force of the European Society of Cardiology, 1996). The number of RR-intervals within one minute translates to the heart rate, which is commonly expressed in bpm (Task Force of the European Society of Cardiology, 1996). Alternatively, the heart rate can be converted into the interbeat interval (IBI), which reflects the time between two R-peaks in ms. Changes in heart rate are commonly analysed as mean changes between conditions (Kreibig, 2010) or regarding their temporal characteristics in analyses of time series (Aghabozorgi, Seyed Shirkhorshidi, & Ying Wah, 2015). Advantages and weaknesses of these approaches are discussed in section 3.2.3.

In addition to changes in heart rate, the variability of one's heart rhythm can be analysed. Based on IBIs, a large number of indices can be derived that characterize different aspects of HRV. Measures of HRV are easily accessible by fully automated software packages and therefore frequently applied, but the validity and reliability of HRV indices highly depends on methodological considerations (Laborde, Mosley, & Thayer, 2017). To begin with, measures of HRV are subject to many influencing factors such as age, gender, weight, height, habitual levels of alcohol and nicotine consumption as well as the intake of medication and hormonal contraception (Larbode et al., 2017). When these factors are taken into account, studies on the retest reliability of HRV report highly comparable results for intervals of six month (Hallman, Srinivasan, & Mathiassen, 2015) and further indicate that HRV is partly heritable (Neijts et al., 2014). These characteristics turn HRV into a valuable measure to assess the flexibility of autonomic adaptations (Thayer & Lane, 2009)

Secondly, the informative value of HRV depends on the selected approach for the calculation of indices. Approaches towards HRV can be divided into three main branches: time-domain methods, frequency-domain methods and non-linear methods (Task Force of the European Society of Cardiology, 1996). Non-linear methods find little application in current psychophysiological research (Laborde et al., 2017) and do not find application in this thesis. Therefore, they are not discussed further. Time-domain methods provide straight-forward indices that describe the variability of a heart rate recording during a specified time window. The two most prominent measures are calculated from the standard deviation of normal-to-normal intervals (SDNN) and from the square root of the mean squared differences between

successive NN-intervals (root mean square of successive differences, RMSSD; Task Force of the European Society of Cardiology, 1996). While SDNN reflects the sum of cyclic components that are responsible for HRV during the recorded time window (Task Force of the European Society of Cardiology, 1996), RMSSD represents beat-to-beat changes in heart rate that are mediated by parasympathetic activity (Shaffer et al., 2014; Task Force of the European Society of Cardiology, 1996). In addition to its clear interpretability as indicator of vagal activity, RMSSD is less influenced by respiration than other measures of HRV (Hill, Siebenbrock, Sollers, & Thayer, 2009), which makes it the parameter of choice in many studies on HRV (Kemp et al., 2017).

In contrast to time-domain methods, frequency-domain measures cannot be derived from IBIs directly but require the transformation of the signal into the frequency space by use of a Fast Fourier Transformation or autoregressive modelling (Laborde et al., 2017). In the course of a power spectral density analysis, a decomposition of the signal into different frequency bands and calculation of the respective power (i.e. explained variance) of each frequency band provides information on the cyclic components present in a specific recording of heart rate (Task Force of the European Society of Cardiology, 1996). In short-term recordings of five minutes of resting heart rate, the power of three frequency bands can be determined: the very low frequency (VLF) component encompassing frequencies below 0.04 Hz, the low frequency (LF) component ranging from 0.04 to 0.15 Hz and the high frequency (HF) component ranging from 0.15 Hz to 0.4 Hz (Task Force of the European Society of Cardiology, 1996). These HRV components are dependent on one's heart rate, thus they should not be compared among individuals unless normalized units are computed (Billman, Huikuri, Sacha, & Trimmel, 2015). Normalized units of LF and HF reflect the relative power of each component proportional to the total power minus the VLF component (Task Force of the European Society of Cardiology, 1996). While HF has consistently been linked to parasympathetic activity and highly correlates with RMSSD (Task Force of the European Society of Cardiology, 1996), LF represents a combination of sympathetic as well as parasympathetic influences (Palma & Benarroch, 2014). This dual influence on LF leads to difficulties in the interpretation of LF and also on the ratio of LF and HF (LF/HF), which by some researchers has been used as indicator of the balance between SNS and PNS activity (i.e. sympatho-vagal balance; Billman et al., 2015). However, due to the unclear physiological origin of LF and consequentially LF/HF, parasympathetic measures of HRV (i.e. HF and RMSSD) are currently recommended (Laborde et al., 2017). Since respiratory effect occur within a similar frequency band as HF, HF is more vulnerable to respiratory effects than

RMSSD (Hill et al., 2009; Laborde et al., 2017). Correction for respiratory influences may remove modulatory effects of the CAN, for respiratory and cardiac functions have shared central nervous influences (Laborde et al., 2017; Thayer et al., 2012). In line with these considerations, RMSSD was selected as measure of vagally mediated HRV in the second empirical study of this thesis.

3.2.3 Methodological considerations on heart rate analyses

In research on the physiological underpinning of emotions, heart rate is the most frequently used measure of cardiovascular functions (Kreibig, 2010). Commonly, mean heart rate and standard deviation over a specific time period are calculated and compared to a baseline condition during which the experimental influence is not present (Kreibig, 2010; Novak, Mihelj, & Munih, 2012). However, comparisons of mean changes are hardly able to capture the temporal dynamics of heart rate changes in emotional experiences and underestimate the potential for time shifts between individuals (Hollenstein & Lanteigne, 2014). The emergence of an emotion does not necessarily coincide with the onset of a potentially emotive stimuli, but rather depends on one's perception and interpretation of the situation at hand (Verduyn, Delaveau, Rotgé, Fossati, & Van Mechelen, 2015). Therefore, designs with fixed resting and experimental conditions possibly misestimate the extent of change in heart rate. Analyses of time series instead of mean changes have the potential to overcome this limitation and provide more detailed information on the dynamics of autonomic adaptations during emotional experiences (Aghabozorgi et al., 2015). Additionally, the investigation of time series makes it possible to address the question of homogeneity of psychophysiological responses and allows to determine more fine-grained subtypes of psychophysiological responses to emotive stimuli that would be masked by mean numeric changes. First evidence for concordance of heart rate trajectories during emotional experiences has been provided by Golland et al. (2014), yet the correlation between heart rate time series observed during an emotive movie only reached a small to medium effect. This low concordance could stem from diverse heart rate response pattern, such as an increase of heart rate in one person when confronted with an emotive stimulus while a second person shows a deceleration of heart rate. By data-driven clustering of heart rate time series, the second empirical study aimed at identifying subtypes of homogeneous heart rate responses during emotions. This switch to trajectories instead of mean changes and the acknowledgement of interindividual variation of heart rate responses fosters the understanding of psychophysiological changes in social cognition.

4 Aims and research questions

The presented overview of the current literature on social cognition points out the paramount importance of socio-cognitive processes for social interactions and therefore an individual's social integration in major domains of life. While previous research provided profound knowledge on many behavioural components of social cognition and their neural correlates, technical and conceptual advances paved the way for more differentiated and methodologically innovative studies. The aim of this cumulative thesis is to contribute to these advances by portraying neural, psychophysiological and behavioural facets of social cognition in healthy individuals and people with epilepsy. In two empirical studies, socio-cognitive functions such as emotion perception and empathy as well as their central nervous and autonomic correlates are investigated. By combining latest methodological approaches in neuroimaging and psychophysiology with ecological and innovative study designs, this thesis offers a multimodal perspective on social cognition.

Preceding the empirical part, a theoretical study that contributes to this thesis is presented. In this theoretical study, socio-cognitive dysfunctions in people with MTLE are contextualised with emphasis on the potential impact of these deficits on the social life of affected individuals. The daily relevance of socio-cognitive deficits as well as intra- and interindividual determinants of social functioning are discussed. This study provides a framework for the following two empirical studies and highlights the importance of social cognition for one's well-being and social integration. Based on this theoretical embedding of social cognition, three research questions arose for the empirical part of this thesis.

4.1 Research question one

The perception of emotions from facial expressions is a crucial building block for efficient social interactions and a major functional domain of social cognition. Current models on the neural substrate of facial emotion perception point out that this function relies on multiple multi-lobar pathways with key involvement of the amygdala. Behavioural deficits in facial emotion recognition as well as alterations of activity of the underlying neural pathways have consistently been reported in people with MTLE. However, the intrinsic FC among brain regions involved in emotion perception has not yet been studied in MTLE.

Therefore, the first research question of this thesis was if – and to what extent – the intrinsic functional network architecture supporting facial emotion perception differs between individuals with and without MTLE. This research question was pursued in the first empirical

study, in which intrinsic functional networks involved in the perception of dynamic fearful faces were depicted by means of fMRI and contrasted between people without epilepsy, those with MTLE and individuals with epilepsy with seizure not originating from the mesial temporal lobe.

4.2 Research question two

Physiological adaptations constitute a key component of emotions and arise from the continuous interplay of the central and autonomic nervous system. Recordings of psychophysiological signals offer a window into the bodily substrate of emotions without disturbance of the emotional experience. Currently, the lively debate on the specificity of psychophysiological adaptations in emotions calls for methodological approaches that are best suited to capture the complex psychophysiological responses to emotive stimuli. In addition, there is an urgent need for ecological yet standardized paradigms that overcome limitations of previous attempts such as the presentation of photographs or imagination of emotional experiences.

Research question two targets the extent of interindividual variability of psychophysiological adaptations during emotional processing. In order to investigate the physiological component of emotions as lifelike as possible, the second empirical study relied on the presentation of a highly emotive and realistic motion picture. Analyses of heart rate were chosen due to the heart's capacity for quick and sustaining adaptations in response to the motion picture, thus offering the possibility to study the temporal dynamics and diversity of psychophysiological adaptations.

4.3 Research question three

Psychophysiological adaptations do not only emerge as part of genuine emotional responses to one's environment, but are also part of the empathic sharing of emotions. While this link is firmly established on the conceptual level, studies on the role of empathy in emotions are sparse. Furthermore, HRV has been introduced as a potential marker of emotional and autonomic flexibility, which would facilitate the empathic sharing of affective states. Although HRV has been related to prosocial concern and ToM abilities, it's informative value regarding a person's tendency to empathize with others remains unclear.

Targeting these gaps, research question three aims at the roles of empathy and HRV in emotional processing. In the second part of the second empirical study, the association between changes in heart rate during the perception of an emotive motion picture and empathy as well

as HRV are investigated. Building upon the finding of interindividual variability of heart rate responses in the first part of this study, it is further examined whether these associations hold true when changes in heart rate are analysed across subgroups of different heart rate trajectories during emotive scenes or if a differentiated analysis of subgroups is indicated.

5 Theoretical study: Why epilepsy challenges social life

Steiger, B. K., & Jokeit, H. (2017). Why epilepsy challenges social life. *Seizure - European Journal of Epilepsy, 44,* 194-198. https://doi.org/10.1016/j.seizure.2016.09.008

5.1 Abstract

Social bonds are at the center of our daily living and are an essential determinant of our quality of life. In people with epilepsy, numerous factors can impede cognitive and affective functions necessary for smooth social interactions. Psychological and psychiatric complications are common in epilepsy and may hinder the processing of social information. In addition, neuropsychological deficits such as slowed processing speed, memory loss or attentional difficulties may interfere with enjoyable reciprocity of social interactions. We consider societal, psychological, and neuropsychological aspects of social life with particular emphasis on socio-cognitive functions in temporal lobe epilepsy. Deficits in emotion recognition and theory of mind, two main aspects of social cognition, are frequently observed in individuals with mesial temporal lobe epilepsy. Results from behavioural studies targeting these functions will be presented with a focus on their relevance for patients' daily life. Furthermore, we will broach the issue of pitfalls in current diagnostic tools and potential directions for future research. By giving a broad overview of individual and interpersonal determinants of social functioning in epilepsy, we hope to provide a basis for future research to establish social cognition as a key component in the comprehensive assessment and care of those with epilepsy.

5.2 Quality of life is social

If you have close friends and confidants, friendly neighbours and supportive co-workers, you are less likely to experience sadness, loneliness, low self-esteem and problems with drugs, eating or sleeping (Helliwell & Putnam, 2004; Szemere & Jokeit, 2015). In fact, this 'social capital' has been found to impact positively on health, morbidity and mortality (Helliwell & Putnam, 2004; Szemere & Jokeit, 2015). Quality social networks (i.e. not Facebook) and support have also been found to be of great importance, acting as a buffer against the impacts of stress exposure in mental and physical health conditions (Thoits, 2011).

Many epidemiological studies have revealed that each of the major determinants of quality of life: employment, social interactions, family relationships, and experiential activities, are at considerable risk in patients with epilepsies (Sherman, 2009). Moreover, epilepsy patients apparently have an increased risk of having impaired social cognitive skills and suffering from communication problems and interpersonal difficulties (Broicher & Jokeit, 2011) Here, we provide an overview of disease-related factors that can influence social functions in epilepsy. We will discuss societal, psychological, and neuropsychological aspects of social life with particular emphasis on socio-cognitive functions in temporal lobe epilepsy.

Social difficulties in epilepsy are not restricted to adulthood. Already in childhood, children with epilepsy have been found to exhibit lower social competence than children without epilepsy (Russ, Larson, & Halfon, 2012). Upon reaching adulthood, those who formerly suffered with epilepsy as children, are often found to have very high rates of social problems, even if they are intellectually within the normal range (Camfield & Camfield, 2007; Szemere & Jokeit, 2015). Such deficits in social functioning can contribute to difficulties in developing relationships and remaining in employment and thus, participating in life as a member of a family, community and culture (Roder, Mueller, & Schmidt, 2011; Szemere & Jokeit, 2015), which in turn affects quality of life. Therefore, social functioning should be of paramount consideration when aiming to improve quality of life in epilepsy throughout the lifespan.

Studies of social functioning in epilepsy have been subject to many major shifts in perspective. More than half a century ago, epilepsy was seriously stigmatised as a disorder that stamps the personality into an 'epileptic personality' surrounded by a 'social abscess' (Guerrant, Anderson, Fischer, Weinstein, Jaros, & Deskins, 1962; Szemere & Jokeit, 2015). Norman Geschwind was one of the first modern neurologists to develop elaborated neuroscientific concepts to explain the increased prevalence of certain behavioural abnormalities as signs of brain dysfunction (Szemere & Jokeit, 2015).

However, beginning in the 1970s, the social and psychological turn in psychiatry and related disciplines may have resulted in a tendency to neglect the neurological basis and overrate the social and psychological underpinnings of certain symptoms affecting social competencies. The following decades were characterised by tremendous efforts to destigmatise patients with epilepsy and empower them (Szemere & Jokeit, 2015).

To date, it is unclear to what extent difficulties in social competences arise from psychosocial conditions or underlying deficits caused by epilepsy-related brain lesions (Szemere & Jokeit, 2015). From a psychological perspective, the effects of stigma, role and experience restrictions, the effects of parental overprotectiveness and fear of seizures (Jacoby et al., 2005) can all impact on social engagement as well as the ability to learn and practice social knowledge and rules (Szemere & Jokeit, 2015). The significantly enhanced prevalence of psychiatric disorders such as depression, anxiety, and psychosis in patients with epilepsy additionally contributes to risk of impaired social relations (Dunn, Austin, & Harezlak, 2007).

Even though psychological factors such as social stigma likely contribute to difficulties in establishing and maintaining interpersonal relationships, people with epilepsy can suffer from impairments in social functioning that cannot be explained by psychological causes alone. Therefore, it is crucial to examine social functioning from multiple perspectives. Although social deficits are not always readily apparent in the majority of patients, signs of poor social amalgamation can permeate all spheres of social life in patients with epilepsy (Szemere & Jokeit, 2015). People with epilepsy are generally found to have fewer social supports compared to those without this condition, are less likely to marry, have fewer children (Jalava & Sillanpää, 1997), have lower rates of employment (Strine, Kobau, Chapman, Thurman, Price, & Balluz, 2002) and cite lack of social engagement and difficulty in developing satisfying interpersonal relationships as common problems (Helliwell & Putnam, 2004; Schmitz, 2007; Szemere & Jokeit, 2015; Thorbecke, 2007). Though interpersonal problems surely do not apply to every person with epilepsy, their far-reaching influence on quality of life deserves clinicians' and researchers' close attention.

5.3 Epilepsy and the social brain

Taking a traditional neuropsychological perspective, it is plausible that cognitive impairment can give rise to social difficulties (Szemere & Jokeit, 2015). Reductions in information processing speed and capacity may prevent a smooth social encounter irrespective of whether the slowing or limitation in capacity is due to post-ictal impairment, side effects of antiepileptic drugs or an underlying brain lesion (Szemere & Jokeit, 2015). Moreover,

attentional and executive deficits including heightened distractability and lowered inhibition may disrupt the fluidity of verbal and non-verbal communication. Having memories in common acts as social glue for couples, family, and close friends and can impel the wish to share future activities together (Szemere & Jokeit, 2015). However, patients with temporal lobe epilepsies in particular frequently suffer from impaired autobiographical memory (McAndrews, 2012). Thus, transient and chronic cognitive impairment in patients with epilepsies itself is a risk factor for poor social integration.

A contemporary perspective comes from neuroscience and the relatively new area of social cognition, also termed social neurosciences (Szemere & Jokeit, 2015). Social cognition is defined as information processing that contributes to the correct perception and interpretation of affective and mental states, dispositions and intentions of another individual (Brothers, 1990; Szemere & Jokeit, 2015). Social cognition encompasses a wide range of functions involved in the processing of social cues. It can be divided into perception and recognition of emotions on the perceptual level, and into more advanced processes of theory of mind (ToM): the inference of mental states, intentions and beliefs of others as well as the prediction of their behaviour based on these mental states (Mitchell & Philips, 2015). Social interactions depend on the efficient processing of social information at the perceptual and at the advanced level in order to ensure smooth communication and a shared understanding of social situations (Szemere & Jokeit, 2015).

These socio-cognitive functions cannot be linked to one specific brain region, but instead rely on distributed networks (Amft et al., 2015). Therefore, impairment of socio-cognitive functions can arise from lesions throughout these networks. While deficient processing of socially relevant information can be found in many types of epilepsy (Stewart et al., 2016), temporal lobe epilepsy (TLE) is the most common and most uniform type of epilepsy and will therefore serve as the focus of our overview on social cognition and its putative relevance for patients' daily lives.

5.4 Multimodal recognition of emotion

Deficits in social cognition in people with TLE can be identified at the basic level of emotion recognition. The face acts as a major source of information in social interactions and provides a wealth of cues for inferences about age, gender, identity, emotions and intentions (Jack & Schyns, 2015). For this reason, most studies on emotion recognition have applied tasks that target facial emotion recognition (FER). In a recent meta-analysis, Bora and Meletti (2016) analysed FER in adult TLE patients either before or after surgical intervention. In both pre- and

postsurgical patients, the recognition of facial expressions was diminished for all six basic emotions (anger, disgust, fear, happiness, sadness, and surprise). The largest effects were found for the recognition of fear, whereas effects for happy and surprised faces were small. At least in cross-sectional studies, FER performance did not differ before and after resection of the mesial temporal lobe. With regard to laterality, poorer FER abilities were found in right-sided TLE for the recognition of fear, disgust, and sadness, whereas no difference was found in anger, surprise and happiness compared to left TLE. Impairments found at the group level were at best medium, with TLE patients obtaining FER scores at most 20% lower than healthy controls (Monti & Meletti, 2015).

When analysing deficits on an individual level, great interindividual variability exists among patients, and substantial deficits have been detected in 30 to 50 percent of patients (Bonora et al., 2011; Meletti et al., 2009). While poor FER performance has been observed repeatedly, the influence of clinical variables is still unclear. In their meta-analysis, Bora and Meletti (2016) found no significant association between FER abilities and age at seizure onset or the presence of hippocampal sclerosis. Contrary to this meta-analytic finding, it has been suggested that patients with epilepsy onset at a young age (<5years) and patients with a long duration of the disease appear to be more heavily impaired in FER (Monti & Meletti, 2015). This assumption derived from studies of adult TLE patients was supported by a study examining children between 8 and 16 years of age with either right- or left-sided TLE or fronto-central epilepsy (Golouboff et al., 2008). Impairments in FER were already present in approximately 25% of the children in all three epilepsy groups. On closer look, groups differed in their recognition performance for specific emotions: TLE children showed difficulties specifically for fear, and impaired recognition of happiness was present in children with fronto-central epilepsy. In children with right-sided TLE, impaired fear recognition was associated with the extent of psychopathological symptoms. Interestingly, half of the children with a history of febrile seizures during infancy displayed substantial FER deficits for fear, whereas only one child without febrile seizures showed borderline fear recognition. These findings indicate that the integrity of mesiotemporal structures is crucial for the development of perceptual socio-cognitive functions. However, the number of studies on the specific influence of disease onset remains small, and longitudinal studies are needed to clearly delineate the developmental course and impairment of FER.

Furthermore, current research is somewhat limited by the low diversity of stimuli employed in experiments measuring FER. Most studies rely on the presentation and subsequent recognition of static black-and-white photographs of faces, yet these paradigms are only a crude

approximation of the processes necessary in daily life interactions. In a more realistic study design, Tanaka et al. (2013) tested FER abilities using short movie clips displaying basic emotions. Consistent with studies using photographs, they found slightly lower recognition rates for TLE patients than healthy participants that were most pronounced for the facial expressions of fear, sadness and disgust. Still, there remains a great need for new, innovative study designs to capture FER in a more naturalistic way. More complex facial expressions such as shame or guilt also have yet to be examined.

Facial expressions are not only frequently presented in behavioural studies; they are also often used in functional MRI (fMRI) studies exploring the neural response to emotional faces. This paradigm plays a special role in TLE pre-surgical evaluation of amygdala functionality (Schacher, Haemmerle, et al., 2006). Alterations of activity in response to fearful faces have been found for the ipsilateral amygdala (Toller et al., 2015) and also for more widespread occipital, temporal and frontal regions (Labudda et al., 2014). Furthermore, activity of the amygdala has been linked to ratings of fear expressed by faces (Labudda et al., 2014) and empathetic concern in a self-report questionnaire (Toller et al., 2015). Additional studies are needed to infer the behavioural relevance of these fMRI differences during the processing of emotional faces.

Emotions can not only be deduced from faces, but also from voices based on prosody or from vocal bursts such as screams, moans or laughter. Although fewer studies have focussed on auditory emotion recognition, deficits have also frequently been reported in TLE (Broicher, Kuchukhidze, et al., 2012). Rates of coinciding deficits in visual and auditory emotional recognition vary between studies and range from 25% (Fowler et al., 2006) to 36% (Bonora et al., 2011), indicating that multimodal deficits occur in some patients, but modalities can be impaired independently as well. Why some patients display emotion recognition deficits in multiple modalities is still unclear. Bonora et al. (2011) argue that patients with disease onset in childhood, and thus with a long duration of ongoing epileptogenic activity over the lifespan, are at particular risk for multimodal emotion recognition deficits.

Apart from the classical approach of facially or vocally expressed emotions, emotion recognition can also be tested using more unconventional paradigms. In studies presenting pieces of music with differing emotional tones, worse recognition of the expressed emotion has been found for patients after anterior temporal lobe resection (Gosselin et al., 2005). When asked about the arousal caused by the musical excerpts, right TLE patients perceived scary music as less stimulating, and, compared to healthy controls, sad excerpts were rated as less relaxing. Left TLE patients indicated that peaceful music appeared less relaxing to them than it

did to healthy individuals. Valence of the musical pieces was not rated differently by TLE patients and healthy controls. It would have interesting to discover whether TLE patients draw less pleasure from the musical excerpts due to their impaired recognition of the implied emotional tone and altered experience of arousal. Such a loss of satisfaction from pleasurable activities like listening to music could reduce patients' quality of life.

Traditional studies on emotion recognition, during which patients have to rate, match or label emotional expressions, have been criticised for neglecting the patient's emotional experience while perceiving emotive stimuli. In order to measure this emotional experience, patients could be asked about their perceived arousal and valence of emotive stimuli (Hennion, Sequeria, et al., 2015). When confronted with fearful faces, Labudda et al. (2014) found lower ratings of perceived fear in TLE patients. However, their perceived arousal in response to these fearful faces did not differ from that of healthy controls. Mirroring this finding, Hennion et al. (2015) reported equal levels of arousal related to unpleasant images in TLE and healthy participants, whereas arousal was higher for TLE patients when perceiving neutral pictures. Higher arousal was furthermore correlated with elevated levels of apathy, which could be interpreted as perception bias in emotional processing in TLE patients. However, alterations of arousal were not linked to further psychosocial variables. So far, no definite conclusion about the emotional experience of patients can be drawn, but incorporating such measures might be helpful in understanding their subjective perception of social stimuli.

5.5 Theory of Mind

It is not sufficient to merely recognize the emotions of another individual on a perceptive level to successfully engage in beneficial social interactions. More complex socio-cognitive functions are necessary to infer the mental states of others and to predict their future behaviour based on their intentions, beliefs and emotions. Neuropsychological tests of these ToM functions usually present patients with situations that closely resemble social interactions typical of daily life, thus ToM deficits are likely to strain social bonds.

Impaired ToM functions have frequently been found in TLE patients, and effect sizes have been found to exceed the impairments observed in FER (Bora & Meletti, 2016). Hennion et al. (Hennion, Szurhaj, et al., 2015) showed that TLE patients struggled to deduce beliefs and emotions in stories in which protagonists unintentionally commit social blunders (faux-pas) or to understand sarcastic comments. These ToM deficits were correlated with lack of social support and affective disturbances. Interference of intentions and emotions in a story-based task was found to be impaired in TLE patients but not in patients with idiopathic generalized

epilepsy (Realmuto et al., 2015); however, the latter group also showed mild deficits in emotion recognition.

Giovagnoli et al. (2013) found poorer ToM abilities in TLE patients, but also in patients with frontal lobe epilepsy as compared to healthy controls. The two groups did not differ from each other in their abilities to detect and understand faux-pas. Patients who performed better on this task were reported to use more efficient coping strategies in response to stressful events and perceived their quality of life higher than patients with weaker ToM abilities. However, an association between ToM abilities and quality of life has not consistently been found (Broicher, Kuchukhidze, et al., 2012). The importance of ToM for one's daily life was further demonstrated in Wang et al.'s study (Wang et al., 2015) that examined ToM in a large sample of therapy-refractory TLE patients. TLE patients performed worse in understanding false belief, implied meaning, faux-pas and cartoon ToM stories. ToM deficits in the faux-pas test also predicted poor social functioning such as social engagement, leisure activities and instrumental living skills in patients. Together with the severity of psychiatric symptoms, ToM further predicted low interpersonal relationships, difficulties in communication, and employment status (Wang et al., 2015).

Although these findings are based on subjective self-report questionnaires, they demonstrate a link between the ability to infer the mental states of others and social functioning in TLE patients. Problematically, many TLE patients are not adequately aware of their own neuropsychological impairments in this area (Giovagnoli, 2013), thus clearly limiting the validity of self-report measures in this population. Given the difficulties inferring the mental states of others, it is questionable if such patients have sufficient insight into their own mental states. This concern is underpinned by heterogeneous findings from self-report questionnaires on empathy in TLE patients. In studies where patients were asked to rate cognitive and affective aspects of empathy, findings range from lower empathetic concern for others in TLE (Toller et al., 2015), to lower cognitive, but not affective, empathy (Hennion, Szurhaj, et al., 2015), to no difference at all between TLE patients and controls (Broicher, Kuchukhidze, et al., 2012). Correspondence between self-report questionnaires and behavioural variables is often low (Broicher, Kuchukhidze, et al., 2012).

This points out that more appropriate measures of empathy and social functioning, such as third-party reports from family members, close friends or co-workers, should be implemented to better determine the actual influence of ToM deficits in a patient's daily life. Of course, it is possible that behavioural deficits detected in neuropsychological examinations appear worse than patients' socio-cognitive functions in their familiar surrounding actually are.

On the other hand, the impact of these deficits might be underestimated due to inadequate test procedures and lack of objective evaluation of everyday socio-cognitive abilities.

5.6 Perspectives

As discussed, the reasons for difficulties with social competence and functioning are multifaceted in epilepsy (see Figure 1), and at present there are no known therapeutic programs for this population that focus on deficits in social interactions (Szemere & Jokeit, 2015). To overcome the diagnostic discrepancy between neuropsychological findings and psychosocial measures of daily life, it is first necessary to gain a thorough understanding of social cognition as a multifaceted neuropsychological domain. While many studies have tried to characterize either basic or higher socio-cognitive functions in TLE, few attempts have been made to unravel the relationship between these levels of social cognition.

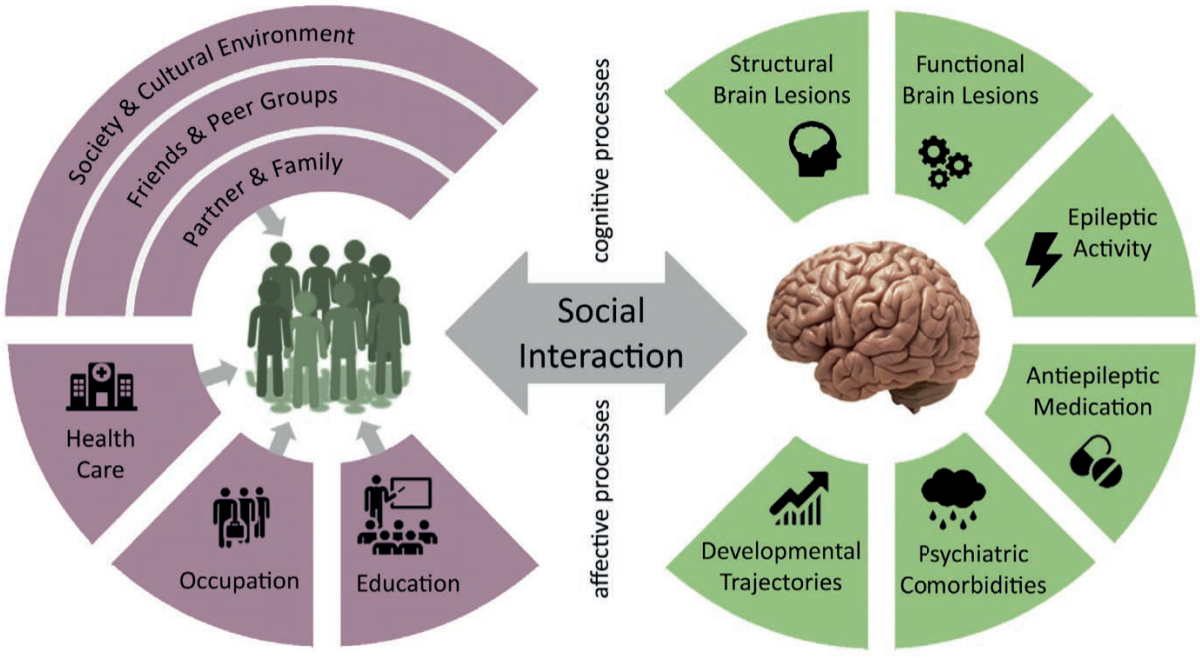

Figure 1. Individual and interpersonal determinants of social functioning in epilepsy.

Emotion recognition and ToM abilities are strongly entwined from a theoretical point of view, and an efficient interplay of perception and interpretation is needed for adaptive social behaviour (Mitchell & Philips, 2015). Unfortunately, even studies with a comprehensive assessment of socio-cognitive functions fail to report correlations between various aspects.

Broicher et al. (Broicher, Kuchukhidze, et al., 2012) showed an association between emotion recognition and performance in the Iowa Gambling Task. Moreover, patients scoring high in emotion recognition showed more appropriate inferences of intentions and emotions when watching a movie clip of animated geometrical shapes whose movements implied social behaviour. However, emotion recognition and other ToM abilities such as the cognitive and affective understanding of faux-pas as well as ascribing mental states to people based on their eyes were independent of each other. In line with these findings, Amlerova et al. (2014) failed to find an association between changes in emotion recognition and changes in ToM abilities after epilepsy surgery. For the time being, the relationship between different processes of social cognition remains elusive, and it is still unclear how other neuropsychological processes such as processing speed or working memory influence socio-cognitive processes and social functioning in real life.

In conclusion, socio-cognitive deficits have been well established in a subgroup of TLE patients, but our understanding of the relationships among domains of socio-cognitive functions and its representations in the central and autonomous nervous system is astonishingly small. We have to keep in mind that the process of successful and enjoyable social interactions is characterized by reciprocity, smooth social encounters, mutual adjustment, temporal and emotional synchronisation, and entrainment. The presentation of photographs and sheets of paper with faux-pas stories, therefore, only represent our initial efforts to establish social cognition within neuropsychology. We call attention to the necessity of bridging the gap between behavioural findings obtained in highly standardized study settings and the processing of the enormous wealth of social cues in real life. Currently, it is not known how the observed socio-cognitive deficits seen in TLE patients translate to the enjoyable but demanding processing of social information in areas of life as diverse as employment, romantic and family relationships, or friendships. We hope that future research will bring forth new and differentiated diagnostic and therapeutic approaches that will allow social cognition to become a key component in the comprehensive assessment and care of people with epilepsy.

6 Empirical studies

1. Steiger, B.K., Muller, A.M., Spirig, E., Toller, G., Jokeit, H. (2017). Mesial temporal lobe epilepsy diminishes functional connectivity during emotion perception. *Epilepsy Research* 134, 33–40.

2. Steiger, B. K., Kegel, L. C., Spirig, E., Jokeit, H. Dynamics and diversity of heart rate responses to a disaster motion picture. Submitted to *Emotion,* under revision.

6.1 Study 1: Mesial temporal lobe epilepsy diminishes functional connectivity during emotion perception

6.1.1 Abstract

Objectives: Unilateral mesial temporal lobe epilepsy (MTLE) has been associated with impaired recognition of emotional facial expressions. Correspondingly, imaging studies showed decreased activity of the amygdala and cortical face processing regions in response to emotional faces. However, functional connectivity among regions involved in emotion perception has not been studied so far.

Methods: To address this, we examined intrinsic functional connectivity (FC) modulated by the perception of dynamic fearful faces among the amygdala and limbic, frontal, temporal and brainstem regions. Regions of interest were identified in an activation analysis by presenting a block-design with dynamic fearful faces and dynamic landscapes to 15 healthy individuals. This led to 10 predominately right-hemispheric regions. Functional connectivity between these regions during the perception of fearful faces was examined in drug- refractory patients with left- (n = 16) or right-sided (n = 17) MTLE, epilepsy patients with extratemporal seizure onset (n = 15) and a second group of 15 healthy controls.

Results: Healthy controls showed a widespread functional network modulated by the perception of fearful faces that encompassed bilateral amygdalae, limbic, cortical, subcortical and brainstem regions. In patients with left MTLE, a downsized network of frontal and temporal regions centered on the right amygdala was present. Patients with right MTLE showed almost no significant functional connectivity. A maintained network in the epilepsy control group indicates that findings in mesial temporal lobe epilepsy could not be explained by clinical factors such as seizures and antiepileptic medication.

Conclusion: Functional networks underlying facial emotion perception are considerably changed in left and right MTLE. Alterations are present for both hemispheres in either MTLE group, but are more pronounced in right MTLE. Disruption of the functional network architecture possibly contributes to deficits in facial emotion recognition frequently reported in MTLE.

6.1.2 Introduction

Mesial temporal lobe epilepsy (MTLE) is the most prevalent form of refractory epilepsy in adults, and is now considered as a complex network disease that affects widely distributed brain regions organized in networks in the afflicted hemisphere (Berg et al., 2010; Jokeit et al., 1997). Consistent with structural and functional abnormalities extending far beyond the mesial temporal lobe (Bernhardt et al., 2013), deficits in neuropsychological functions relying on large-scale networks such as memory (Bell, Lin, Seidenberg, & Hermann, 2011), language (Bartha-Doering & Trinka, 2014) and executive functions (Stretton and Thompson, 2012) are a common characteristic of MTLE. Growing evidence suggests that people with MTLE are also at considerable risk for deficits in social cognition that threaten a patient's social bonds and quality of life (Steiger and Jokeit, 2017). Impairments are frequently reported in emotion perception with results being most consistent in facial emotion recognition (Monti and Meletti, 2015). While evidence at the behavioural level is quickly expanding, the functional networks underlying emotion perception in MTLE have received little detailed study.

Perceiving social signals efficiently is crucial for the inference of mental and emotional states of others and successful behavioural adaptation (Mitchell and Phillips, 2015). Interpersonal behaviour in complex social environments is to a large part guided by faces, which convey a wealth of visual social stimuli (Haxby et al., 2000). Functional MRI studies have revealed a distributed set of regions supporting facial emotion perception (Fusar-Poli et al., 2009). In addition to occipital and basal temporal regions, vital aspects of emotion perception such as processing of biological motion, dynamic facial expression and eye gaze have been associated with the anterior (aSTS) and posterior superior temporal sulcus (pSTS) as well as the inferior frontal gyrus (IFG; Duchaine and Yovel, 2015). Furthermore, the amygdala is implicated in the general detection of salience and rapid evaluation of emotive stimuli (Janak & Tye, 2015). An efficient interplay of these regions is required to meet the demands of social interactions (Duchaine and Yovel, 2015).

In MTLE, altered activity of these regions involved in emotion perception may contribute to deficits in the recognition of facial expressions (Monti and Meletti, 2015). Brain imaging studies have consistently revealed lesser activation of the amygdala ipsilateral to seizure onset during the processing of fearful faces (Benuzzi et al., 2004; Schacher, Haemmerle, et al., 2006; Toller et al., 2015). However, weaker responses to emotional faces were also found for bilateral FFA (Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004) and lateral temporal regions (Labudda et al., 2014). These functional alterations that lie beyond the assumed epileptogenic lesion support the understanding of MTLE as a network disease and

point to the need for further studies on the underlying functional network architecture of emotion perception.

The afore-mentioned fMRI studies investigated brain activation while participants were actively engaged in emotion perception. However, the brain is always intrinsically active and forms patterns of synchronized intrinsic activity even when one is resting. These patterns are the building blocks of the brain's intrinsic functional network architecture (Buckner et al., 2013). It can be inferred from measures of functional connectivity (FC), which is defined as the statistical dependency between BOLD-signal fluctuations (Biswal et al., 1995; Buckner et al., 2013). Furthermore, the intrinsic network architecture is influencing functional connectivity during specific processes such as the perception of social signals (Cole et al., 2014; Smith et al., 2009). Studies on intrinsic FC suggest that the amygdala is part of a large and spatially distributed functional network linked to perception, affiliation and aversion behaviour (Bickart et al., 2014). Changes to these networks have been reported in people with MTLE at rest and during tasks. Altered intrinsic FC of the left amygdala was found in left MTLE, whereas right MTLE was associated with extensive FC differences of both amygdalae (Doucet et al., 2013). During emotion perception, lateralized task-modulated FC alterations were reported for people with left and right MTLE by applying an independent component analysis (Broicher, Frings et al., 2012). However, FC between specific regions as putative cause of deficits in emotion perception has yet to be investigated.

We assume specific functional network alterations of the amygdala and functionally associated areas during facial emotion perception in people with MTLE. Based on previous findings (Broicher, Frings et al., 2012; Doucet et al., 2013), we hypothesize predominantly ipsilateral differences of FC in left MTLE and rather bilateral FC alterations in right MTLE.

6.1.3 Methods

Participants

For this study, 48 patients diagnosed with unilateral drug-refractory focal epilepsy syndromes were recruited from consecutive inpatient admissions to the Swiss Epilepsy Center. Patients were referred to the fMRI examination as part of a comprehensive pre-surgical evaluation during 2007 and 2013. The sample consisted of 16 patients with left MTLE, 17 patients with right MTLE, and 15 patients with focal epilepsy with structural lesions not located within the mesial temporal lobe (extra MTLE) to control for general effects of epilepsy and its treatment with antiepileptic drugs (AED). To be included in either MTLE group, the following inclusion criteria applied: unilateral hippocampal sclerosis (HS) validated on T1 and T2

weighted high-resolution MR images, unilateral temporal seizure onset shown by continuous interictal and ictal video-EEG monitoring with either scalp or intracranial electrodes (15.2% intracranial), coinciding side of HS and side of seizure onset, no additional structural cerebral pathologies, and valid fMRI examination. Inclusion criteria for the extra MTLE group were unilateral focal epilepsy syndrome with seizure onset in frontal (33.3%), temporo- lateral (46.7%), and occipital lobes (20%), diagnosis of drug-resistant localization-related epilepsy syndrome (lesional = 66.7%, non-lesional = 33.3%), confirmed diagnosis by neurological examination, continuous interictal and ictal video-EEG monitoring with scalp and intracranial (20.0% intracranial) electrodes and structural MRI.

All patients were treated with antiepileptic drugs (AEDs) at the date of the fMRI examination. Patients were either on monotherapy (left MTLE = 25.0%, right MTLE = 64.7%, extra MTLE = 40.0%) or polytherapy (left MTLE = 75.0%, right MTLE = 35.3%, extra MTLE = 60.0%). All patients underwent a psychiatric interview during their pre-surgical evaluation. Mild to moderate levels of depression or anxiety disorders did not lead to exclusion because of the high prevalence of affective disorders in patients with epilepsy (Garcia, 2012). Antidepressant drugs were prescribed to 31.3% of left MTLE patients, 5.9% of right MTLE patients and 20.0% of extra MTLE patients. For all patients, language lateralization was determined by use of fMRI during the pre-surgical workup as described by Woermann et al. (2003).

Additionally, 30 healthy participants (healthy control group, HC) were recruited. HC participants were free of neurological or psychiatric disorders, did not report alcohol or substance abuse, and did never undergo chemotherapy. The HC group was randomly divided into two groups of 15 participants each. Data of the first group (HC-task) was used to delineate ROIs based on the activity in the fMRI localizer task. For the analysis of functional connectivity, data of the second group (HC-conn) was included.

The study was approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients and controls provided written informed consent.

Table 1

Demographic and clinical characteristics for each group.

	Group					Statistics	*P*
	HC-task (*n*=15)	HC-conn (*n*=15)	LTMLE (*n*=16)	RMTLE (*n*=17)	EXTRA (*n*=15)		
Demographic variables							
Sex, m / f	8 / 7	5 / 10	7 / 9	8 / 9	8/7	$\chi^2(4) = 1.6$	0.798
Age, mean years (*SD*)	38.95 (12.0)	37.50 (13.17)	33.02 (12.88)	44.64 (10.97)	29.78 (13.79)	$F(4) = 3.3$	0.015
Clinical variables							
Age at epilepsy onset, median years (range)	-	-	11 (2 – 34)	15 (1 – 44)	11 (3 – 27)	$H(2) = 0.2$	0.864
Duration of epilepsy, median years (range)	-	-	18.5 (2 – 47)	25 (4 – 51)	14 (2 – 40)	$H(2) = 0.9$	0.635
AEDs, median n per day (range)	-	-	2 (1-3)	1 (1-3)	2 (1-3)	$H(2) = 4.8$	0.238
Depressive symptoms, % *n*	-	-	37.5	29.4	40.0	$\chi^2(2) = 0.4$	0.804
Antidepressants, % *n*	-	-	31.3	5.9	20	$\chi^2(2) = 3.9$	0.145
Language lateralization (*n* typical/atypical/unclear)	-	-	11/4/1	14/2/1	12/2/1	$\chi^2(4) = 1.2$	0.871

HC-task, healthy control group for activation analysis; HC-conn, healthy control group for the connectivity analysis; LMTLE, patients left mesial temporal lobe epilepsy; RMTLE, patients right mesial temporal lobe epilepsy; EXTRA, patients with extratemporal lobe epilepsy.

Functional magnetic resonance imaging

Image acquisition. All structural and functional scans were performed on a 3.0-T Philips scanner (Philips Medical Systems, Best, The Netherlands) using a 32-channel head coil. Head motion was restricted by foam padding. Anatomical images were obtained with a T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence with the following parameters: 176 sagittal slices, thickness = 1 mm, skip = 0 mm, repetition time (TR) = 8.1 ms, echo time (TE) = 3.7 ms, flip angle = 8°, field of view (FOV) = 240 × 240 mm2, isotropic voxel size = 1 mm^3. Functional data was acquired using a gradient echo planar imaging (EPI) sequence with 18 coronal slices orthogonal to the hippocampus covering temporal and frontal lobes, TR=1500ms, TE=35ms, flip angle=75°, FOV=220×220 mm^2 and voxel size = 2.75 × 2.75 × 4 mm.

Experimental design. This study applies an fMRI paradigm, which was previously validated in healthy participants as well as in patients with unilateral epilepsy to evoke activation in regions involved in processing of dynamic fearful faces (Schacher, Haemmerle, et al., 2006; Toller et al., 2015). The paradigm corresponds to a block design of visual stimuli with

two alternating conditions of 24 s duration each. Eight blocks of each condition were presented. The condition of interest (dynamic fearful faces) consisted of 75 short episodes from horror movies showing faces of actors. In each clip, actors expressed intense fear for 2–3 s. During the second condition, 72 clips of landscapes with matched duration were shown to ensure ongoing visual stimulation. Participants could see the stimuli in an overhead mirror facing toward a screen on which the paradigm was projected. Participants were instructed to focus on the actor's eye region when faces were visible. Unlike paradigms which implement static faces or drawings, this naturalistic paradigm based on dynamic movie clips likely evokes activation that closely resembles face processing in real life. This enabled us to investigate FC modulated by dynamic face processing in a less artificial way.

Imaging preprocessing. Functional imaging data were preprocessed using Statistical Parametric Mapping (SPM) 12 (http://www.fil.ion.ucl.ac.uk/spm/). The first 16 volumes were discarded to ensure stabilization of the magnetic field. Slice-timing correction was performed to correct for differences in acquisition time within each volume. Realignment was carried out in a two-step procedure with a first realignment to the first and second to the mean image. The T1-weighted images were co- registered to the functional scans and segmented into gray matter, white matter and cerebrospinal fluid. To perform spatial normalization into MNI space, the DARTEL toolbox was used (Ashburner, 2007). A study-specific gray matter template (N = 78) was created by DARTEL, this template was transferred into MNI space, and the transformation parameters were applied to all structural and functional scans (all 2 × 2 × 2 mm voxels). Normalized functional scans were smoothed with a 6 mm full-width at half-maximum Gaussian kernel. A high-pass filter with a cut-off of 0.008 Hz was applied.

Activity analysis. To identify potential regions of interest (ROI) for the connectivity analysis, regions with stronger activation during the perception of fearful faces than during the landscapes were identified using SPM 12. For this analysis, only half of the HC group (HC-task) was considered. Analyses of FC were carried out with the second half of the control group (HC-conn) to avoid distortion of the FC analysis toward an overestimation of FC in HC. A general linear model was built for each participant with regressors for each condition. Regressors of interest were created for the two conditions (fearful faces/landscapes) and convolved with a hemodynamic response function. To control for participants' head movement, estimated motion parameters were included as regressors of no interest. The contrast of interest (fearful faces > landscapes) was calculated for each participant and forwarded to the second-

level random-effect group analysis. A one-sample t-test with age as a nuisance covariate was calculated to detect regions of stronger BOLD signal during fearful faces compared to landscapes. Results were considered significant at a threshold of $P_{FWE} < 0.05$ with a cluster extent threshold of k = 4 contiguous voxels. Spherical ROIs with a radius of 4 mm were centered on the peak MNI coordinates of significant activation clusters (see Fig. 1 and Table 2). This analysis serves the purpose to identify regions involved in the given task, but will not be covered in the discussion specifically.

Functional connectivity analysis. In order to investigate intrinsic FC modulated by dynamic face processing, FC among the ROIs derived from the activity analysis was analyzed using the CONN fMRI connectivity toolbox by Whitfield-Gabrieli and Nieto-Castanon (2012, v15h) in SPM12. Denoising of the data is crucial for FC analyses and comprised several steps. Time-series were high-pass filtered with a threshold of 0.008 Hz, despiked and detrended. Physiological processes such as heart rate and respiration are a potential source of low-frequency noise and pose a challenge to FC analyses since they potentially influence the BOLD signal (Chang, Cunningham, & Glover, 2009). To reduce the influence of physiological noise, a component-based noise correction method (CompCor; Behzadi et al., 2007) implemented in CONN was applied. In order to analyze FC during face processing, task effects induced by the block design need to be taken into account. If task effects were not removed from the data, observed FC would rather reflect effects driven by task-induced co-activation to a stimulus, for which functional activation analyses were better suited. By regressing out task effects and their first temporal derivates alongside with motion parameters, resulting FC measures reflect a combination of intrinsic FC as well as task-evoked FC modulations (Cole et al., 2014; Fair et al., 2007; Whitfield-Gabrieli & Nieto-Castanon, 2012). This approach allows us to investigate intrinsic FC of the face processing network modulated by the perception of dynamic fearful faces. We did not analyse FC during the control condition (perception of landscapes) because we focus on the present functional network architecture in the context of dynamic emotion perception.

Statistical analyses

Bivariate correlation coefficients were estimated to represent the association between the time courses of the ten ROIs on the first level and were used to analyze group differences in functional connectivity at the second level. Because of the overall attenuation of the BOLD signal in people with epilepsy, which is most likely induced by antiepileptic drug treatment (Jokeit, Okujava, & Woermann, 2001), results are reported before ($p_{uncorrected} < 0.05$) and after ($p_{FDR} < 0.1$) correction for multiple comparison including results classifying as statistical trends after FDR correction.

ROI-to-ROI functional connectivity was calculated during blocks of dynamic fearful faces to examine networks involved in face processing for each group with age as regressor of no interest. Correlation coefficients were tested one-sided to depict a network of regions with significant FC during the perception of fearful faces. To assess the general influence of duration of epilepsy, the correlation with ROI-to-ROI FC during fearful faces was determined for each patient group while age and age at epilepsy onset were controlled. To investigate the influence of age at epilepsy onset, the correlation with ROI-to-ROI FC during fearful faces was calculated and corrected for age and duration of epilepsy.

6.1.4 Results

Participant characteristics

Demographic and clinical data of the four groups for the connectivity analysis and of the HC-task for the derivation of ROIs are presented in Table 1. Comparisons of the five groups revealed that groups differed only with respect to age. Therefore, age was included as covariate of no interest in further analyses. The three patient groups did not differ in age at epilepsy onset, duration of epilepsy, presence of depressive symptoms, language lateralization as well as medication with antiepileptic or antidepressant drugs (all $p > 0.05$).

Task-related activity analysis

To determine regions of the temporal and frontal lobes involved in processing of fearful faces in HC-task, the contrast fearful faces > landscapes was calculated. Random effects analysis revealed nine clusters where the BOLD response was stronger for fearful faces than for landscapes. These regions included the right anterior insula, bilateral amygdala, right anterior and posterior superior temporal sulci (STS), right precentral gyrus (PG), bilateral periaqueductal gray (PAG), right IFG and right putamen (all $p_{FWE} < 0.05$, see Table 2). The

cluster of the PAG contained peaks for each hemisphere, thus two ROIs were created for the PAG.

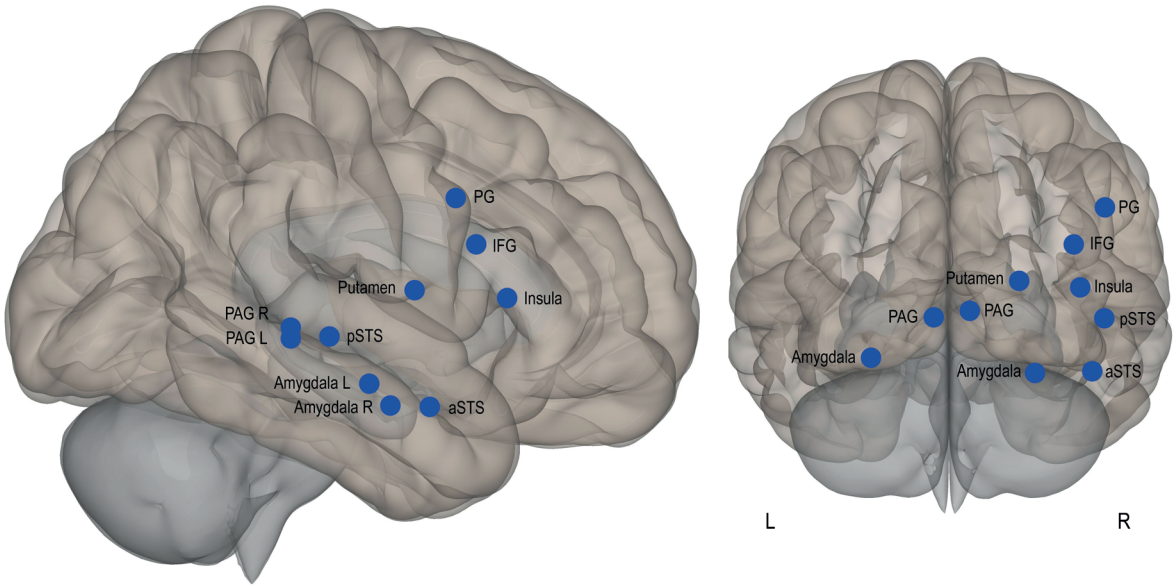

Figure 1: Regions of interest. Location of the regions of interest (ROIs) based on the activation analysis with stronger activation for dynamic fearful faces compared to landscapes. ROIs are displayed from a right lateral and from a coronal perspective. Spherical ROIs with a radius of 4 mm were placed on right and left amygdala, right and left periaqueductal gray (PAG), right anterior superior temporal sulcus (aSTS), right posterior superior temporal sulcus (pSTS), right putamen, right anterior insula, right inferior frontal gyrus (IFG), and right precentral gyrus (PG).

Functional connectivity during emotion perception

During the perception of dynamic fearful faces, HC-conn showed positive FC within a widespread network of cortical and subcortical regions (see Table 3). Regarding amygdala FC, bilateral amygdalae showed significant correlations with the posterior STS, while only the right amygdala was correlated with the anterior insula. Results for the three patient groups are shown in Table 4. In patients with left MTLE, significant positive correlations were found for the right amygdala with pSTS, aSTS and PG, as well as between pSTS and Putamen. Patients with right MTLE only showed significant FC between PAG L and aSTS. In extra MTLE patients, activity in the amygdalae was correlated with each other, yet they showed differing functional connections to further regions. Results for all four groups are visualized in Fig. 2.

To examine the influence of the duration of epilepsy, its main effect on FC during the perception of dynamic fearful faces was calculated. Across all three groups, duration of epilepsy had a negative main effect on the FC between PAG R and IFG, thus longer duration of epilepsy was associated with weaker FC (left MTLE $t(76) = -3.17$, $p_{FDR} = 0.020$; right MTLE $t(76) = -3.08$, $p_{FDR} = 0.027$; extra-MTLE $t(76) = -2.58$, $p_{FDR} = 0.005$). Furthermore, a trend for weaker FC between right PAG and left PAG with longer duration of epilepsy was found for right MTLE ($t(76) = -2.58$, $p_{FDR} = 0.054$). Age at epilepsy onset had a negative main effect in the left MTLE group on FC between PAG L and PG ($t(76) = -3.16$, $p_{FDR} = 0.021$) as well as PG and PAG R ($t(76) = -2.56$, $p_{FDR} = 0.056$). No significant effects of age at epilepsy onset were found for right MTLE or extra MTLE.

Table 2

Significant activation pattern evoked by the perception of fearful faces compared to landscapes in healthy controls.

Region	Side	*k*	MNI coordinates			*T*	*p-FWE*
			x	y	z		
Anterior insula	R	45	44	24	6	7.94	0.002
Amygdala	R	127	30	-6	-22	7.59	< 0.001
Amygdala	L	109	-24	-12	-16	7.50	< 0.001
Superior temporal sulcus, anterior	R	29	48	4	-22	7.47	0.014
Precentral gyrus	R	43	52	10	32	7.19	0.003
Periaqueductal gray	L	102[a]	-4	-32	-4	6.83	< 0.001
Superior temporal sulcus, posterior	R	43	52	-22	-4	6.49	0.003
Periaqueductal gray	R	102[a]	8	-32	-2	6.43	< 0.001
Inferior frontal gyrus	R	49	42	16	20	6.16	0.002
Putamen	R	21	24	0	8	6.13	0.037

k = cluster size

[a] The cluster of the PAG contained one peak per hemisphere. Two ROIs were derived from this cluster.

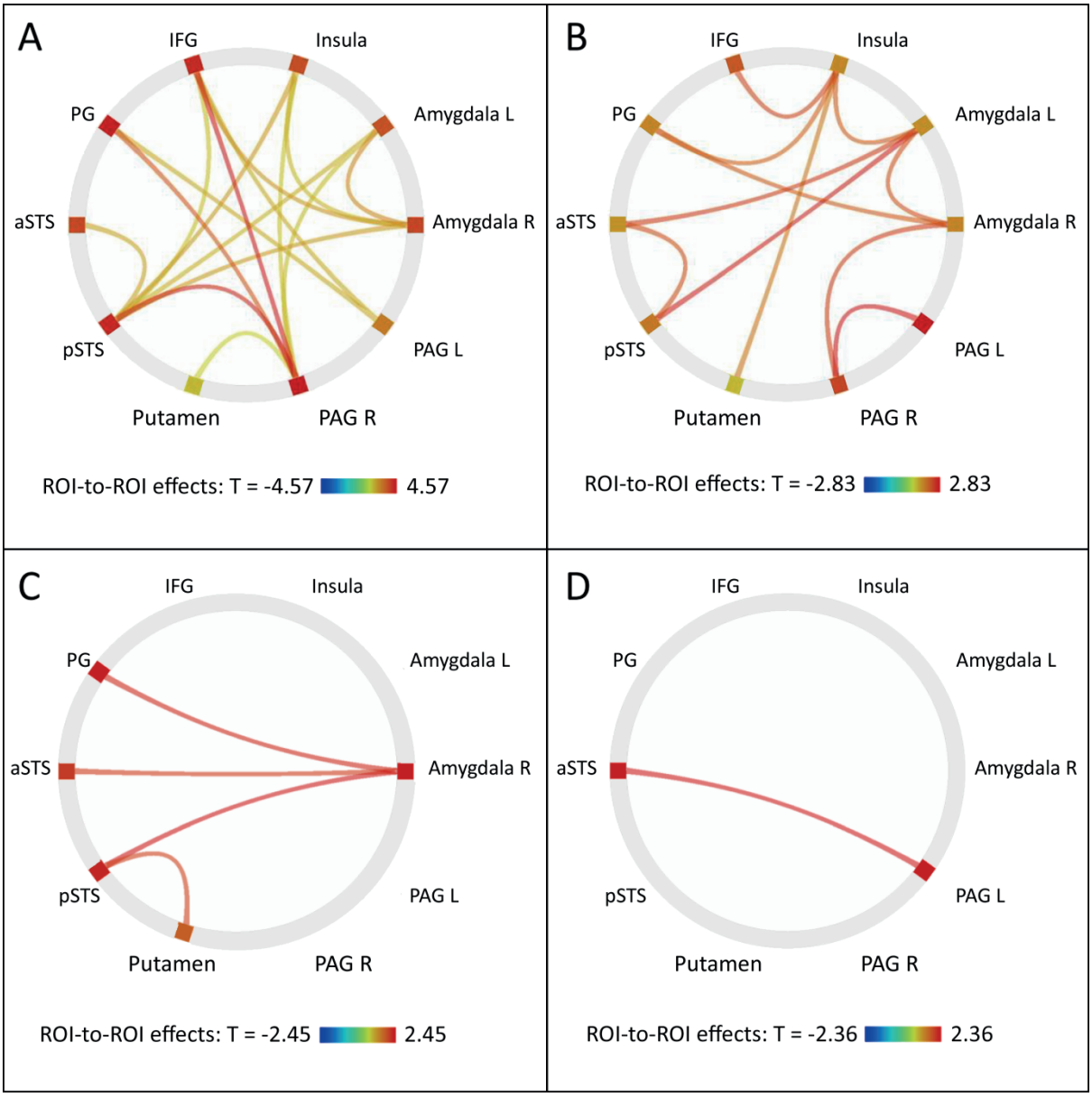

Figure 2: Functional connectivity during emotion perception. Visualization of functional connectivity among the ten ROIs during the perception of fearful faces for each group. Connections are depicted if significant at $p_{uncorrected} < 0.05$ and $p_{FDR} < 0.1$ to represent meaningful findings and trends. If not indicated by the letters L and R for bilateral ROIs, ROIs are located in the right hemisphere. Height of the T-values is indicated by color as shown in the color bar. A: healthy controls; B: extra MTLE, C: left MTLE; D: right MTLE; L: left hemisphere, R: right hemisphere; aSTS, anterior superior temporal sulcus; MTLE, IFG, inferior frontal gyrus; mesial temporal lobe epilepsy; PAG, periaqueductal gray; pSTS, posterior superior temporal sulcus; PG, precentral gyrus.

Table 3

ROI-to-ROI functional connectivity for healthy controls during fearful faces.

Seed ROI	Target ROI	*T*	*p-uncorrected*	*p-FDR*
Amygdala L				
	Amygdala R	2.61	0.005	0.049
	pSTS R	2.00	0.025	0.099
	PAG R	1.86	0.033	0.099
Amygdala R				
	Amygdala L	2.61	0.005	0.038
	Inferior frontal gyrus	2.38	0.01	0.038
	pSTS	2.28	0.013	0.038
	Anterior insula	1.95	0.027	0.061
Inferior frontal gyrus R				
	PAG R	4.57	< 0.001	< 0.001
	Amygdala R	2.38	0.01	0.045
	PAG L	2.12	0.019	0.056
	pSTS R	1.84	0.035	0.078
PAG L				
	Inferior frontal gyrus R	2.12	0.019	0.085
	Precentral gyrus R	2.11	0.019	0.085
PAG R				
	Inferior frontal gyrus R	4.57	< 0.001	< 0.001
	pSTS R	4.33	< 0.001	< 0.001
	Precentral gyrus R	3.46	< 0.001	0.001
	Amygdala L	1.86	0.033	0.065
	Anterior insula R	1.82	0.036	0.065
	Putamen R	1.60	0.056	0.085
Precentral gyrus R				
	PAG R	3.46	< 0.001	0.004
	PAG L	2.11	0.019	0.085
pSTS R				
	PAG R	4.33	< 0.001	< 0.001
	Anterior insula R	2.34	0.011	0.034
	Amygdala R	2.28	0.013	0.034
	aSTS R	2.21	0.015	0.034
	Amygdala L	2.00	0.025	0.044
	Inferior frontal gyrus R	1.84	0.035	0.052

Note. Seed ROIs were listed if they have significant correlations with at least two target ROIs. Seed ROIs with one correlation were not reported if this correlation was already covered by the corresponding target ROI. ROI, region of interest; FDR, false discovery rate; aSTS, anterior superior temporal sulcus; pSTS, posterior superior temporal sulcus; PAG, periaqueductal gray; FC, functional connectivity.

Table 4

ROI-to-ROI functional connectivity for the three epilepsy groups during fearful faces.

Seed ROI	Target ROI	*T*	*p-uncorrected*	*p-FDR*
Left MTLE				
Amygdala R				
	pSTS R	2.45	0.008	0.052
	Precentral gyrus R	2.32	0.012	0.052
	aSTS R	2.15	0.017	0.052
pSTS R				
	Amygdala R	2.45	0.008	0.074
	Putamen R	2.09	0.020	0.091
Right MTLE				
PAG L				
	aSTS R	2.36	0.010	0.093
Extra MTLE				
Amygdala L				
	pSTS R	2.75	0.004	0.034
	aSTS R	2.43	0.009	0.039
	Amygdala R	2.18	0.016	0.044
	Anterior insula R	2.10	0.020	0.044
Amygdala R				
	PAG R	2.39	0.010	0.064
	Amygdala L	2.18	0.016	0.064
	Precentral gyrus R	2.06	0.021	0.064
Anterior insula R				
	Inferior frontal gyrus R	2.33	0.011	0.065
	Amygdala L	2.10	0.020	0.065
	Precentral gyrus R	2.05	0.022	0.065
	Putamen R	1.83	0.036	0.081
PAG R				
	PAG L	2.83	0.003	0.027
	Amygdala R	2.39	0.010	0.043
Precentral gyrus R				
	Amygdala R	2.06	0.021	0.098
	Anterior insula R	2.05	0.022	0.098
aSTS R				
	Amygdala L	2.46	0.009	0.061
	pSTS R	2.26	0.013	0.061
pSTS R				
	Amygdala L	2.75	0.004	0.034
	aSTS R	2.26	0.013	0.061

Note. Seed ROIs were listed if they have significant correlations with at least two target ROIs. Seed ROIs with one correlation were not reported if this correlation was already covered by the corresponding target ROI. ROI, region of interest; FDR, false discovery rate; MTLE, mesial temporal lobe epilepsy; aSTS, anterior superior temporal sulcus; pSTS, posterior superior temporal sulcus; PAG, periaqueductal gray;

6.1.5 Discussion

In this study, we investigated task-modulated intrinsic FC of the amygdala and functionally associated areas in the context of dynamic emotion perception. In healthy individuals, our analysis revealed a highly interconnected functional network of temporal, frontal, striate, limbic and brainstem regions. This is consistent with previous research on facial emotion perception (Duchaine and Yovel, 2015) and highlights the importance of the interplay between the amygdalae and lateral temporal and frontal areas. However, this network was considerably altered in individuals with either right- or left-sided MTLE.

Differences in functional network architecture in MTLE

In line with our initial hypothesis, right MTLE patients demonstrated a largely diminished functional network during emotion perception. Significant FC was only observed between left PAG and aSTS. While the PAG is associated with autonomic regulation and processing of salient stimuli such as pain or emotions (Linnman, Moulton, Barmettler, Becerra, & Borsook, 2012), the aSTS is implicated in processing of eye gaze, head movement and multimodal integration (Duchaine and Yovel, 2015). FC among these regions has rarely been described (Coulombe, Erpelding, Kucyi, & Davis, 2016) and its interpretation remains speculative.

The absence of further significant functional connections highlights the importance of the integrity of the right mesial temporal lobe for emotion perception. Although activation studies examining healthy individuals support a bilateral processing of emotional faces (Fusar-Poli et al., 2009), the detrimental effect of a right-sided mesial temporal epileptogenic network indicates a major role of these structures in the processing of emotional faces. Additionally, right-sided MTLE patients showed not only weakening of FC of the right amygdala, deviations from the healthy network were also present for the left amygdala and for functional connections not involving the mesial temporal lobe. These widespread disruptions are in line with the new understanding of epilepsy as a network disease (Berg et al., 2010; Jokeit et al., 1997).

Comparing patients with left- and right-sided MTLE, more extensive alterations of the functional network architecture are present in right- sided MTLE. This is consistent with larger disruptions of intrinsic FC at rest in right- than left-sided MTLE (Doucet et al., 2013). In our analysis, patients with left MTLE still displayed significant FC within a network centered on the right, non-epileptogenic amygdala. However, functional connections differed from the network observed in HC. One major difference concerns the functional connection between right amygdala and anterior insula, which was not significant in either MTLE group.

Involvement of the anterior insula in emotion perception has not consistently been found in healthy individuals (Foley, Rippon, Thai, Longe, & Senior, 2012; Furl et al., 2013) and possibly depends on task characteristics such as the experience of social emotions and prediction of emotional states of others (Lamm & Singer, 2010). Interestingly, an activation analysis by Toller et al. (2015) showed preserved activation of the anterior insula in response to dynamic fearful faces for left- and right-sided MTLE patients. This divergence between activation and FC might indicate that while both regions are still engaged in the processing of emotional faces, their functional connection is considerably weakened.

Additionally, differences in the functional network were also present for lateral temporal areas. Contrary to the findings in HC, FC between pSTS and anterior insula failed to reach significance in both MTLE groups. Although in left-sided MTLE the pSTS was still functionally connected to the right amygdala, its further connections to frontal, temporal and brainstem regions were not significant in either group. This finding is congruent with previous research of Åhs et al. (2014) in which an attenuation of pSTS activation during emotional face perception in patients after either left or right anterior temporal lobe resection was observed. This was interpreted as missing modulatory input from the resected mesial temporal lobe. Our results suggest that this modulation is already impoverished prior to surgical interventions.

Influence of clinical variables on functional networks

Investigating the influence of clinical variables is essential in chronic diseases such as epilepsy. We did not find a specific influence of the patient's age at epilepsy onset on FC. However, longer duration of disease was associated with significantly weaker FC between right PAG and IFG. Thus, ongoing drug-refractory epilepsy was associated with differences in FC, but not involving connections of the amygdala.

Furthermore, antiepileptic medication is known to exert broad influence on the BOLD signal (Jokeit et al., 2001). The presence of only minor alterations in patients with extratemporal lesions indicates that differences present in MTLE are not induced solely by factors shared among epilepsy patients such as antiepileptic treatment.

Our findings cannot be explained by psychiatric comorbidities as groups did not differ in their rate of psychiatric symptoms or treatment with antidepressants. In fact, patients with right-sided MTLE showed the lowest absolute rate of psychiatric comorbidities despite the largest functional network alterations.

Behavioural relevance of functional network alterations

Impairments in emotion recognition are a frequent feature of MTLE and patients score up to 20% worse than HC (Monti and Meletti, 2015). These moderate behavioural deficits are in contrast to the widespread FC alterations in this work and previous fMRI studies (Labudda et al., 2014; Toller et al., 2015). Two explanations may account for this divergence. Although empathetic concern (Toller et al., 2015) and ratings of fear in dynamic faces (Labudda et al., 2014) have been linked to amygdala activation, behavioural effects are mostly subtle. Since many patients experience their first seizures during childhood, adaptive compensatory changes of the networks disrupted by the epileptogenic network could occur over the course of the disease (Tracy & Doucet, 2015).

Second, many tests on emotion recognition suffer from low ecological validity due to the artificial test situation and the stimuli (i.e. photographs of emotional expressions; Monti & Meletti, 2015; Steiger & Jokeit, 2017). Possibly, the consequences of functional network disruptions fail to find expression in highly standardized neuropsychological assessments, but may yet contribute to psychosocial difficulties frequently occurring in the daily life of patients (Quintas et al., 2012).

Despite this divergence between widespread changes in the functional network architecture and moderate deficits in general emotion recognition, some correspondence can be found. In their meta-analysis of emotion recognition in MTLE, Bora and Meletti (2016) point out that largest impairments were found for the recognition of fear, and this weakness was significantly more pronounced for patients with right- sided MTLE. This is consistent with our finding of altered FC in patients with left and right MTLE as well as more diminished FC in patients with a right-sided epileptogenic network. Since only fearful faces were presented in our study, we cannot infer the general clinical impact of the found network alterations. Still, these coinciding alterations support the assumption of diminished FC as underlying cause of behavioural deficits. How these alterations on the neural level interact with further impeding factors such as social stigma and how they find expression in the daily life of people with epilepsy are yet unanswered questions (Steiger & Jokeit, 2017).

Limitations

This study has some limitations. First, the applied fMRI paradigm is a passive task, and the stimulus material varied in many aspects (e.g. gender and age). That said, our paradigm seems best suited to capture processes of everyday social interactions. Additionally, fearful faces constitute imperative stimuli that initiate automatic processes of emotion perception

(Adolphs, 2008). Second, no behavioural data regarding emotion recognition is available for this study sample. For this reason, clinical implications should yet be derived cautiously, but currently running studies of our group are focusing on closing this gap.

Regarding the analysis of FC, it is unclear to what extent FC measured during task states reflects intrinsic functional networks and how extensively they are modulated by the given task (Cole et al., 2014; Fair et al., 2007). Finally, our fMRI sequence covered frontal, temporal and partly parietal lobes but not occipital areas. This compromise had to be taken in order to maximize signal-to-noise ratio in the amygdala.

Conclusion

We have shown a widespread intrinsic functional network modulated by the perception of dynamic fearful faces that encompasses cortical, subcortical and brainstem regions in healthy individuals. Large network alterations have been found in MTLE patients with either left or right hemispheric epileptogenic networks. Notably, a narrowed functional network centered on the right amygdala was observed in left MTLE, whereas right MTLE patients showed almost no significant FC among the examined regions. Regardless of MTLE lateralization, disruption of FC between amygdala, anterior insula and pSTS of the right hemisphere was present. These alterations may contribute to deficits in emotion recognition in MTLE patients (Monti and Meletti, 2015). However, the discrepancy between extensive FC changes and often subtle behavioural deficits needs to be resolved. We believe that analysing functional network characteristics will be a vital approach to gain a more profound understanding of socio-cognitive impairments in MLTE.

6.2 Study 2: Dynamics and diversity of heart rate responses to a disaster motion picture

6.2.1 Abstract

Emotions are dynamic neuropsychophysiological processes that guide behaviour and serve as crucial signals during social interactions. Measuring their temporal dynamics is an unresolved challenge, but the coupling of autonomic and central nervous processes offers a promising approach. We present a feasible approach to study changes in heart rate during emotions and demonstrate a link to empathy.

First, we investigated the interindividual similarity and temporal dynamics of heart rate responses to an emotive motion picture. Forty healthy participants watched "The Impossible" (109 minutes; Hermida Muñiz et al., 2012) while their heart rate was recorded. Interindividual concordance of heart rate responses was analysed using agglomerative hierarchical clustering analyses to distinguish response patterns throughout the movie and during six highly emotive scenes. This revealed multiple response patterns during emotive scenes.

Second, we analysed how changes in heart rate are linked to self-reported empathy and heart rate variability as indicator of emotional flexibility. We found that the extent of changes in heart rate is positively linked to trait and state empathy. During specific scenes, this relationship was only visible when individuals with homogeneous heart rate response patterns were observed.

In conclusion, our results strongly suggest that heart rate responses to complex social stimuli are not uniform. Therefore, research should favour statistical procedures with the potential to detect interindividual differences. The approach presented in our study allows us to depict interindividual similarity and diversity in emotional autonomic responses and emphasizes the key role of empathy in emotional experiences.

6.2.2 Introduction

Emotions provide meaning to our daily lives, guide thoughts, desires and decisions and serve as important signals for social interactions (Adolphs, 2010; Cacioppo et al., 2000). Although tremendous progress has been achieved in affective neuroscience, measuring and characterizing the experience of emotions is an ongoing challenge. The multitude of determinants of emotions and their potential for affective responses that are interindividually disparate have yet to be acknowledged in studies on emotional processing (Verduyn et al., 2015). Beyond that, there is a scientific and diagnostic need for practicable approaches for investigating altered emotional processing. Especially, this becomes apparent in light of the high prevalence of disturbed affective processing in many neurological and psychiatric disorders such as temporal lobe epilepsy, fronto-temporal dementia and depression (Steiger & Jokeit, 2017). Moreover, paradigms using naturalistic stimuli, and of consequently higher ecological validity, are rare in the current literature.

To understand human affective processing, one must consider that brain functions evolved under the constant pressure of survival and the need to adapt to increasingly complex social environments (Bradley et al., 2014; Smith et al., 2017). In order to fulfil one's needs in the face of continuously changing external conditions, ongoing adaptation of bodily and mental states is vital (Thayer & Lane, 2000). In this effort, emotions emerge from a constant comparison of an individual's current needs, past experiences as well as challenges and opportunities posed by the environment (Schirmer & Adolphs, 2017; Thayer & Lane, 2000). Although a shared definition of emotions has yet to be agreed upon (Norman, Berntson, & Cacioppo, 2014), consensus exists on the multifaceted nature of emotions: emotions comprise orchestrated changes in central nervous processes as well as adjustments in the peripheral physiology (Smith et al., 2017). Pointing out how indispensable bodily changes are to emotional experiences, Robert W. Levenson (Levenson, 2014) subsumed, "When it comes to emotion, all roads lead to the autonomic nervous system (ANS)".

Adaptive bodily changes are achieved by varying activity of the two subdivisions of the ANS, the sympathetic (SNS) and parasympathetic nervous system (PNS). They originate from brainstem nuclei and convey CNS signals to organs in the periphery to modulate their functions. In return, the SNS and PNS allow the integration of bodily signals to the CNS (Appelhans & Luecken, 2006; Levenson, 2014). This dynamic interplay of CNS and ANS enables top-down influence on bodily functions as well as perception of one's own physiological state to prepare and adapt oneself for the current situation (Critchley & Harrison, 2013). Regarding the CNS, regions involved in the modulation of ANS functions are subsumed as the central autonomic

network (CAN; Benarroch, 1993; Thayer et al. 2009), which largely overlaps with regions implicated in emotional processing and empathy (Amft et al., 2015; Beissner et al. 2013; Bernhardt & Singer, 2012; Bickart et al., 2014).

The desire to characterize physiological changes associated with emotions and possibly deduce emotion-specific patterns has been a driving force in numerous previous studies (Critchley & Harrison, 2013). One of the organs innervated by SNS and PNS with strong functional linkage to emotions is the heart, which has often been the target of such studies (Critchley et al., 2013). In the long-lasting literature on emotion research beginning with William James (James, 1894) and Wilhelm Wundt (Wundt, 1874), changes in heart rate and heart rate variability (HRV) have frequently been demonstrated for a number of emotions (Cacioppo et al., 2000; Kreibig, 2010; Stemmler, 2004). For some emotions, general response tendencies were observed: While happiness, fear and anger are often associated with an increase in heart rate, mixed findings are reported for sadness and disgust (Kreibig, 2010). So far, evidence for consistency and specificity of autonomic responses in emotions is very mixed (Levenson, 2014). Although the subjective difference between boiling with rage and trembling with fear is obvious, it is still under debate if specific autonomic patterns of emotions exist and if so, under which conditions (Norman et al., 2014). The functional capacity of the regions of the CAN, which regulate these psychophysiological adaptations in emotions, is assumed to be reflected by HRV (Thayer et al., 2009). Therefore, HRV is currently interpreted as indicator of autonomic flexibility with strong linkage to emotion regulation and health (Kemp et al., 2017; Shaffer et al., 2014).

We set out to investigate emotional processing in a most ecological yet standardized way. This was achieved by presenting the highly emotive disaster motion picture "The Impossible" (Hermida Muñiz et al., 2012). The presentation of an entire motion picture is a novelty in this field of research and its complexity exceeds the information presented by pictures or short film clips by far. The richness of stimuli in the selected motion picture yields the potential to evoke a broad range of emotions across a time frame of almost two hours.

Our overarching goal was to pursue a methodological approach that acknowledges the many determinants of emotional experiences and has the potential to uncover interindividual differences. Recordings of heart rate during the presentation of the motion picture offered a window into the psychophysiological adaptations in the longer course of emotional experiences. The heart rate provides continuous beat-to-beat information on the joint influence of sympathetic and parasympathetic activity on the heart as consequence of central nervous modulatory processes (Palma & Benarroch, 2014). This allows us to study the temporal

dynamics of heart rate changes throughout the entire movie and during highly emotive scenes. In the first part of this study, a data-driven approach to differentiate distinct patterns of heart rate responses to emotive scenes is presented.

While the analysis of psychophysiological signals offers an integrative perspective on emotional processing, it is challenging to determine the mental underpinning of the observed physiological changes. In a second step, we explored if changes in heart rate as response to the motion picture are a function of an individual's predisposition for empathy. Additionally, we aim to clarify if individuals with larger changes in heart rate report stronger situative feelings of empathy concerning the motion picture. Finally, we investigated the informative value of HRV as global indicator of emotional flexibility (Appelhans & Luecken, 2006).

Interindividual concordance of physiological adaptations in emotional experiences

A major challenge in investigating autonomic responses to emotionally arousing stimuli lies in the nature of emotions themselves. Emerging from the continuous interplay of the CNS and ANS to optimize the match between the individual and the environment, emotions possess an inherently dynamic character as they unfold over time (Quigley & Barrett, 2014; Verduyn et al., 2015). Thus, frequently applied approaches such as comparing averaged bodily signals during highly emotional states to a baseline condition (Codispoti, Surcinelli, & Baldaro, 2008; Fernández et al., 2012; Novak et al., 2012) tend to neglect important aspects of autonomic emotional changes. This shortcoming has recently been addressed by Golland et al. (2014), who investigated interindividual concordance of physiological responses while participants were watching an emotionally arousing movie. With this promising approach, they were able to demonstrate significant correlation between heart rate and electrodermal activity across participants associated with the emotive movie. However, their analyses relied on the premise that individuals show highly similar physiological responses to a stimulus and thus neglected interindividual variations. This assumption is questioned by interindividual differences in ANS reactivity (Quigley & Barrett, 2014; Shaffer et al., 2014) as well the importance of cognitive appraisal in emotions (Barrett, 2016; Thayer & Lane, 2000), which is influenced by the individual's characteristics and past experiences (Verduyn et al., 2015). Therefore, it should be expected that even when individuals are confronted with the exact same external environment, their autonomic adaptations vary due to differences in their internal states. Consequently, analyses neglecting the possibility of interindividual variations run the risk of oversimplifying or underestimating autonomic changes in emotions.

In a first step, we propose a methodological approach for the investigation of long-term dynamic autonomic responses to emotive stimuli that has the potential to portray interindividual differences in physiological responses on different time scales. Our aim was to measure heart rate responses to a full-length emotionally-charged movie and to further aggregate groups of individuals with a shared heart rate response pattern during specific emotive scenes. If uniform dynamic changes in heart rate are induced by the emotive movie, individuals should show highly correlated heart rate time series. We further hypothesized that not only one but different patterns of heart rate time-series emerge during scenes comprising an emotionally charged event. To investigate this, we calculated correlations of heart rate time series for the duration of an entire motion picture. For selected scenes, we intended to identify clusters of heart rate response patterns based on the similarity of time courses between individuals. In sum, this approach enabled us to analyse interindividual concordance of heart rate responses with regard to different time-scales of autonomic responses and the emotive content of specific scenes.

Is empathy a magnifier for vicarious psychophysiological adaptations?

In a second step, we investigated the behavioural relevance of the evoked changes in heart rate during the motion picture. More specifically, our special interest lied on a person's predisposition to empathize with others. In our daily life, we often need to put ourselves in the shoes of others to understand their feelings, motivations and actions to be able to navigate the muddy waters of social life efficiently. The capacity to empathize fosters social coherence (Bernhardt & Singer, 2012), whereas failing to understand and cooperate with others can lead to social disintegration in major life domains like employment, friendships or romantic relationships (Steiger & Jokeit, 2017).

Empathy can be characterized as an affective reaction in response to the affective state of another living being (Walter, 2012). De Vignemont and Singer (2006) proposed a clear-cut definition that was carried on by many colleagues (Bernhardt & Singer, 2012; Lamm et al., 2017). They suggest that by observing or imagining the affective state of another person, an isomorphic affective state is elicited in the observer while the observer knows that the observed person is the source of one's affective state. Although definitions of empathy vary considerably, there is general agreement that the sharing of affective experiences, so-called affective isomorphism, is an essential component of empathy (see Walter, 2012, for a discussion).

Imaging studies suggest that the generation of vicarious affective states relies on the same neural circuits that are activated when one experiences firsthand affective states (Lamm et al., 2017). As a consequence, shared affective states also draw on the modulatory capacities

of the CAN and comprise adaptations of one's physiological state that are equivalent to those in genuine emotions (Critchley et al., 2013). Thus, when empathically sharing the fear of another person, not only do we mirror the CNS activation, but also our own hands become sweaty, our muscles tense and our heart beats faster. These psychophysiological adaptations can be readily measured across various channels (Critchley & Harrison, 2013) and could shed light on this facet of empathy, yet very few studies have seized this opportunity.

Changes in heart rate are a prominent feature in genuine affective processes and can easily be recorded (Kreibig, 2010), and consequentially analyses of heart rate have been the method of choice in studies on empathic affective processes as well. In a recent study, Truzzi et al. (2016) showed that higher empathy and lower autistic traits were associated with higher changes in heart rate during the perception of social but also non-social human interactions. Similar findings were reported by Oliveira-Silva and Gonçalves (2011), who examined changes in heart rate while participants watched short emotive film clips and were then urged to mentally prepare a response they would perform if someone expressed the respective emotion to them. Afterwards, a selection of responses was presented and participants had to declare which of the responses best suited their own. A larger acceleration of heart rate during this response phase was observed in participants who chose highly empathic responses in comparison to participants whose responses reflected less empathy. These first studies suggest that empathy is related to the psychophysiological adaptations involved in the processing of social stimuli. Still, current findings are limited to short film clips of little personal relevance.

Equivalent to the predisposition for empathy as a personality trait (Walter, 2012), stable physiological features that reflect the general efficiency of the interplay of body and brain have been explored. In the past years, HRV has been brought forward as an index of autonomic flexibility and regulatory capacities of the CAN (Smith et al., 2017; Thayer & Lane, 2000). Due to the continuous innervation of the heart by the SNS and PNS, HRV is assumed to reflect the capacity of the CAN to integrate environmental and physiological demands in order to adapt one's physiological state to a specific situation (Appelhans & Luecken, 2006). Especially HRV measures reflecting the parasympathetic beat-to-beat influence at rest (i.e. vagal tone) have been linked to greater cognitive empathy (Quintana et al., 2012), more prosocial behavior (Beffara et al., 2016) and more efficient attentional, perceptual and regulatory processes in social contexts (Park & Thayer, 2014). However, the relation between HRV, empathy and adaptations of heart rate during complex social situations in general is not yet well studied.

In the second part of this study, we strive to extend previous findings on the relationship between empathy and changes in heart rate as response to emotive stimuli. The presentation of

the motion picture "The Impossible" (Hermida Muñiz et al., 2012) offers a standardized paradigm that includes numerous situations to empathize with the protagonists. Empathy was captured twice; prior to the motion picture as personality trait and afterwards as state measure. We hypothesize that individuals with higher trait empathy show larger changes in heart rate during the motion picture than less empathic individuals. Furthermore, we assume that more extensive changes in heart rate are associated with stronger feelings of empathy during the motion picture. As a second goal, we aim to explore the informative value of HRV as a predictor of autonomic and emotional flexibility. We expect that larger HRV at rest is associated with higher trait empathy and more extensive changes in heart rate as well as higher state empathy in response to the motion picture.

6.2.3 Methods

Participants

Female and male participants aged between 18 and 65 years were recruited from volunteer databases from the University of Zurich and via advertisement in local social media. Initially, 45 participants were recruited. This data set will be used as a reference group for clinical populations in future studies, thus a stratified sample according to age and education was selected to provide demographic diversity with regard to gender, age and years of education.

Participants met the following criteria: Swiss German or German as native language or excellent proficiency in German, no medication to treat cardiac arrhythmia or other cardiovascular diseases, no medication with influence on the cardiovascular system such as sedatives or other psychoactive drugs, no known cardiovascular and neurological health conditions, no drug intake during studies in the 30 days preceding this study, no incident of severe head injury or severe diseases of the brain, no abuse of illegal substances, no colour-blindness or hearing impairments. Participants must not have seen the movie which served as stimulus material. Furthermore, participants were asked to refrain from the consumption of alcohol, cannabis and further illegal substances 24h prior to the study. This study was approved by the local ethics committee. All participants provided written informed consent and were reimbursed with 30 Swiss francs.

We could not include data of five participants in the final sample. Two participants were excluded due to irregularities in their heart rhythm that could be indicative for cardiovascular pathologies. In one case, recording of the heart rate was not successful due to technical issues. One participant completed the study procedure but later informed the study staff about his

frequent consumption of cannabis. One additional exclusion was necessary because the participant was not able to comply with the study procedure.

Study procedure

The study was conducted at the Swiss Epilepsy Centre. Participants were tested individually or, if desired, in pairs of two when participants were acquainted for optimal use of resources. Six participants were tested in pairs. A member of the study staff was present throughout the entire study procedure to ensure compliance and provide security. Prior to movie presentation, participants were asked to provide data on their demographics, level and years of education as well as consumption habits regarding alcohol, nicotine and regular medications. Female participants were asked to give information on their menstrual cycle and use of hormonal contraception.

To identify possible vulnerable individuals, all participants were asked whether they themselves or a person close to them ever experienced life-threatening situations or natural disasters. Four out of 40 participants reported such an incident, and it was ensured that they felt comfortable with the movie given the theme of a natural disaster hitting a family. All four participants agreed to watch the movie regardless and assured the study personal that they would alert them if they felt uneasy during the movie.

Prior to and shortly after the movie, blood pressure was measured with a blood pressure monitor (Medisana®, Germany) on the upper arm to control for incidental findings of hypo- and hypertension. Subsequently, participants put on a special t-shirt to record their heart rate. Participants were seated in a comfortable armchair in front of a screen. Distance to the screen was 210 cm, image size on screen was 170 x 75 cm. Sound was provided by two loudspeakers, each placed on one side of the participant, and the volume did not exceed a threshold of 80 dB.

Before the movie started, lights were turned off and participants were asked not to talk or perform excessive movement throughout the movie. Five minutes of resting heart rate were recorded to serve as a baseline from which HRV could be derived. During the baseline, participants sat in an upright position, with knees bent at a 90° angle, breathing spontaneously, without moving or speaking to the study staff. Additionally, this baseline was later used to compare the extent of heart rate change during the baseline and the movie.

Subsequently, the movie was presented. If a toilet break was requested during movie presentation – which once was the case – the movie was paused. The participant took a five-minute break and was then asked to rest for two minutes before the movie was resumed to ensure that changes in heart rate caused by movement were not falsely attributed to emotive

events in the movie. The break did not occur during scenes of interest that were subject to our analyses.

Right after the movie, participants rated their empathic experiences using a study-specific questionnaire. Blood pressure was measured for the second time and participants were allowed to remove the measurement t-shirt. They were reimbursed and thanked for their participation.

Materials

Motion picture. These studies served to investigate short and long-term changes in heart rate that are part of emotional experiences. To meet this aim, stimulus material of sufficient duration and breadth of emotive content had to be selected. The motion picture "The Impossible" (Hermida Muñiz et al., 2012) was chosen for this purpose and was shown to participants in its entirety (109 minutes). It portrays the true story of a family who fell victim to the 2004 tsunami catastrophe in Thailand and thus addresses a dramatic event that most people witnessed through media reports. The family consists of Henry (father), Maria (mother) and their three sons Lucas, Simon and Thomas (from oldest to youngest). During the course of the movie, the family is separated after the impact of the tsunami and struggles for survival, but is finally reunited. A wide range of emotions such as fear, despair, sadness, disgust, surprise, relief and joy are portrayed. The addressed concepts of family cohesion and natural catastrophes are highly emotionally charged and easily relatable. Few romantic and no explicit sexual or interpersonal violent actions are displayed. Additionally, the observed emotive situations gain relevance as participants are introduced to the protagonists' personal story and participants can bond with them over the course of the movie. The combination of extensive information on the protagonists, the possibility to follow their true story for almost two hours and the increased self-relevance stemming from one's own memories on the actual Tsunami catastrophe brings this paradigm closer to real life than commonly applied stimulus material like pictures and short film clips.

Trait and state empathy. Empathy was assessed twice during this study. Empathy as a stable individual disposition was measured with the German version of the Interpersonal Reactivity Index (IRI; Davis, 1983; in German Saarbrücker Persönlichkeitsfragebogen, Paulus, 2009). The IRI is composed of the four scales empathic concern (EC), personal distress (PD), perspective taking (PT) and fantasy (FS). To reduce bias due to social desirability and influences of the experimental setting, participants completed the questionnaire on trait empathy at home prior to study participation.

Additional to the measurement of trait empathy, the empathic experience during the motion picture was assessed with a study-specific questionnaire (movie rating, MR). Participants were asked to rate their experiences on a continuous horizontal scale from "not at all" to "very much" regarding their pleasure ($MR_{Pleausure}$, "How much did you like the movie?"), emotional touch ($MR_{Emotion}$, "How much were you touched emotionally by the movie?"), empathy ($MR_{Empathy}$, "How much did you feel empathy towards the characters?") and bodily reactions (MR_{Body}, "How much did your body respond to the movie?").

Health-related covariates. For further characterization of the study sample, health-related variables were assessed. Participants were asked to indicate their height and weight to calculate the body mass index (BMI). Mean arterial pressure (MAP) was calculated as diastolic pressure + 1/3 (systolic pressure - diastolic pressure) to quantify average arterial pressure during a single cardiac cycle. Sample characteristics are presented in Table 2.

Registration and pre-processing of heart rate

Registration of heart rate was carried out with the Smartex Wearable Wellness System (WWS, Smartex s.r.l., Italy). The WWS is a tightly fitting t-shirt with two textile electrodes located below the pectoral muscle to record participants' heart rate. Data were recorded with a sampling rate of 250 Hz and stored on a small electronic storage device (SEW, CSEM SA, Neuchâtel, Switzerland) attached to the WWS. Synchronization between the recording of physiological data and the presentation of the motion picture was achieved by pressing a button on the recording device SEW at a specified moment. In response to an acoustic cue that was preceded by a count-down, the staff member manually set the marker point. Minimal differences in the timing of the trigger are possible, yet they are eliminated by the steps of subsequent data pre-processing. After the recording session, data were exported and fed into the software package VivoSense (VivoSense® HRV Professional Edition Version 3.0, Vivonoetics, San Diego, CA, USA). After an algorithm-based detection of R-peaks with VivoSense, the resulting R-peaks were visually inspected and manually corrected in cases where R-peaks were misidentified. Afterwards, interbeat intervals (IBI) were calculated. Segments of artefacts due to participants' movements were linearly interpolated if they were shorter than four seconds and excluded from the analysis if artefact-adhesive data exceeded four seconds. Additional automatic artefact correction was used to linearly interpolate physiologically improbable IBIs (heart rate lower than 30 bpm or higher than 220 – years of age). In the case of the participant who requested a break during the movie, the corresponding section of the time series was excised. For each participant, the corrected IBI time series were

then resampled at 1Hz and transformed to measures of heart rate in beats per minute (bpm) to create an evenly spaced time series of heart rate.

Two further steps, which are outlined in Figure 1, were undertaken to prepare heart rate data for group level analysis. First, to correct for interindividual variations in average heart rate as well as long-term time shifts throughout the movie, a temporal detrending was applied. To do so, a 2nd degree polynomial function was fitted to individual time series. Raw time series were subtracted from the 2nd degree polynomial function which led to detrended heart rate residuals. Those residuals represent momentary deviation from the global trend.

In a second step, intraindividual beat-to-beat fluctuations likely not to have been evoked by emotional experiences were filtered out of the detrended time series. This was achieved by applying a temporal Gaussian filtering with a moving smoothing kernel with $\sigma = 8.57$ corresponding to a kernel width of full width at half maximum (FWHM) of 20 seconds. Heart rate changes associated with strong emotional experiences last from seconds to minutes (Kreibig, 2010; Levenson, 2014). Thus, they withstand this temporal smoothing and can even be amplified because non-systematic fluctuations are likely to be filtered out. This approach is not advisable for analyses of heart rate variability measures in the frequency domain such as power in low and high frequencies because frequency based information would be distorted by the pre-processing (Task Force of the European Society of Cardiology, 1996).

Heart rate variability at rest

For the computation of HRV at rest, the corrected ECG time series were converted into IBI time series and fed into the analysis software Kubios (Kubios HRV Version 2.2, Tarvainen, Niskanen, Lipponen, Ranta-aho, & Karjalainen, 2014). The root mean square of successive differences (RMSSD) for the five-minute baseline was calculated as measure of vagal tone that is hardly affected by respiration (Hill et al., 2009; Laborde et al., 2017).

Analyses of whole-movie time series

Analyses of pre-processed heart rate time series as well as analyses of demographic data were carried out with IBM SPSS Statistics for Macintosh V23. To begin with, the extent of heart rate changes was compared between the baseline condition and the movie to demonstrate the potential influence of the emotive stimulus material. Secondly, Pearson correlations among all individual time series were calculated. This serves as a global indicator of whether stimulus material of such temporal extent can provoke consistent changes in heart rate among participants (Aghabozorgi et al., 2015; Novak et al., 2012). Although large variability between

participants that would lead to overall low correlations is to be expected (Verduyn et al., 2015), it is nonetheless possible that some participants show similar responses even throughout the whole movie.

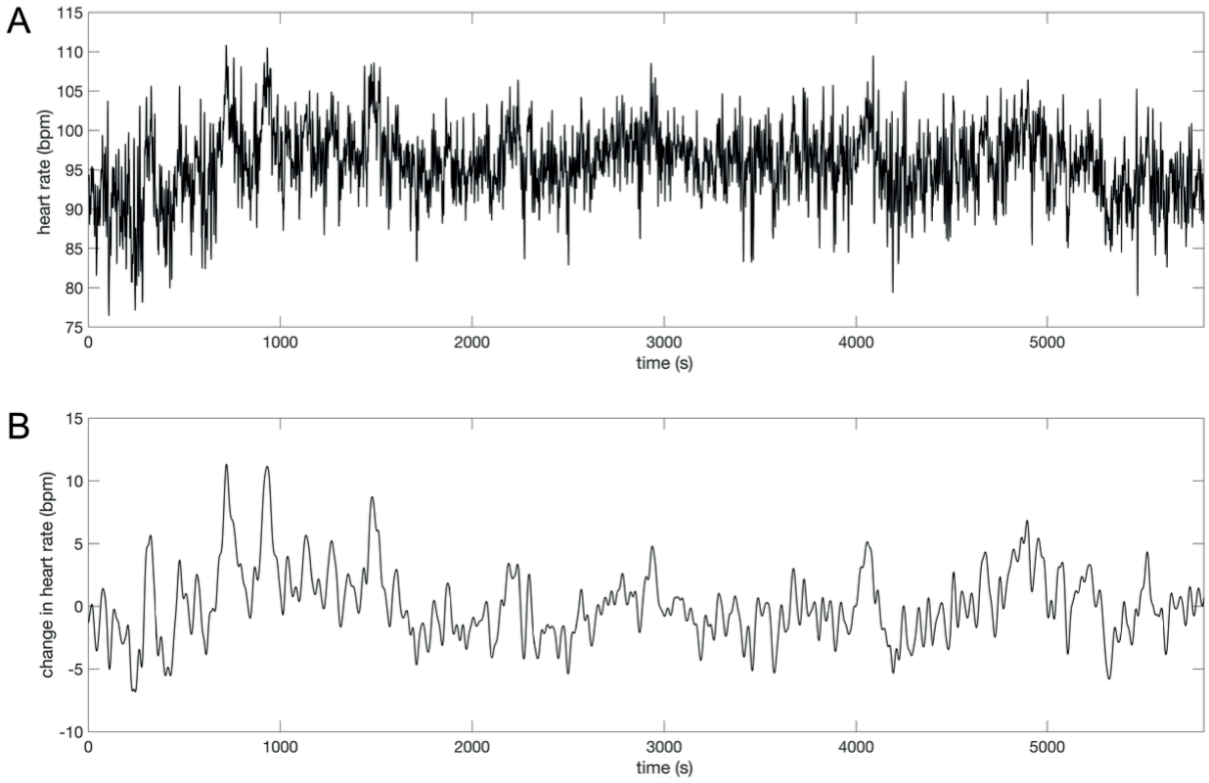

Figure 1. Illustration of the pre-processing pipeline with (A) an individual heart rate time-series resampled at 1 Hz, and (B) the individual time series after detrending with a second-degree polynomial function and temporal smoothing with a Gaussian kernel of FWHM = 20s. After the pre-processing steps, data reflect change in heart rate instead of the real heart rate. bpm, beats per minute; s, seconds.

Selection of emotive scenes

To further investigate the consistency of specific heart rate changes during scenes with a high potential to evoke emotions, six scenes were selected. The scenes covered the turning points in the dramatic composition of the movie and were selected based on a two-step rating procedure. To begin with, three psychologists of the study staff watched the motion picture and marked scenes whenever they experienced strong emotions. If a scene was mentioned by at least two of the three raters, it was considered for the analysis. This led to a selection of 30 scenes. A rating board of five psychologists then assessed the usability of each scene with respect to two criteria. First, scenes had to consist of a highly salient event with associated changes in behaviour, facial expression, vocalization, and posture of the protagonists as well as changes in background sounds in some scenes (e.g. sounds of destruction during the tsunami). Secondly, scenes had to contain dynamic changes of the emotive stimuli so that the plot could be summarized in different phases. Scenes needed to start with a calm phase (phase one, P1), followed by the emotive event (phase two, P2) and a subsequent phase with a change in intensity or in the emotion displayed by the protagonist (phase three, P3). Six scenes fulfilled these requirements and were selected for the following analyses. Due to the limitations imposed by the movie itself, scene composition and duration differed between scenes. A short narration of the plot with associated phases and duration of each of the six scenes are presented in Table 1.

Table 1.

Summary and Characteristics of the Six Emotive Scenes.

Nr	Name	Duration	Plot
1	Tsunami	108 s	The family is spending time at the pool. Maria is reading a book while Henry and the sons play ball in the pool (P1). The peaceful mood is disturbed by a power outage and signs of impending danger such as a heavy breeze and fleeing animals (P2). Palm trees are falling over as the tsunami hits the beach and the pool area. The force of the tsunami destroys houses, tourists are screaming. Maria yells at Henry to save the children, but all family members are hit by the wave and are pulled under water (P3).
2	Rescue	108 s	Maria, Lucas and another boy are recovering up in a tree when Lucas spots a group of locals. He shouts out to them for help (P1). Maria is no longer able to walk. The locals drag her through the fields which are covered with sticks and debris. Maria is screaming in pain because of a heavily bleeding wound on her thigh (P2). One of the men dragging her is maintaining eye contact and speaks soothing words while Maria loses consciousness (P3).
3	Vomit	107 s	Lucas and Maria are resting at the hospital next to an unknown woman lying motionless beside them. Lucas talks to the woman and offers her some clementine (P1). Suddenly, the unknown woman starts to gag and throws up blood and plant parts. Maria first tries to help the woman (P2), but has to vomit heavily herself (P3).
4	Phone call	146 s	Henry is sitting at a bus station with a group of tourists. He tells how he found his two younger sons but does not know the whereabouts of his wife and Lucas. A man offers his phone to Henry so he can call home (P1). Henry calls his father-in-law and learns that Maria has not yet called home. Hearing this, Henry starts to cry heavily and ends the call quickly (P2). The other tourists calm him down and encourage him to call again. Henry calls a second time with more composure and promises to search for Maria and Lucas (P3).
5	Victim reunion	172 s	Lucas is trying to find relatives of victims in the hospital. He walks the aisles and calls out their names (P1). A young boy responds to his calling and learns that his father is alive and looking for him. The boy hugs Lucas in relief and the two boys smile at each other (P2). Lucas runs back to the father and then witnesses their reunion (P3).
6	Family reunion	155 s	Unknowingly, all family members are at the same hospital. Henry had stopped at the hospital to look for Maria and Lucas, but finishes his stop at this hospital and climbs a car which would take him to another clinic. Lucas looks for Henry, whom he spotted in the distance. Meanwhile, Thomas and Simon are taking a break in front of the hospital (P1). Lucas calls out loudly for his father and his cry is heard by his brothers. They rush to him and hug him fiercely (P2). By coincidence, Henry spots his boys, calls out to them and they run towards each other. Henry hugs his sons close (P3).

Note. Nr, number of Scene; P, phase.

Clustering of heart rate time series during emotive scenes

To identify different heart rate patterns in response to the emotive movie scenes, a cluster-analytic approach was chosen. Pre-processed time series served as the basis for these analyses. For each scene, the corresponding heart rate time series were extracted for every participant. Afterwards, clusters of similar time series were determined by an agglomerative hierarchical cluster analysis. First, similarity between participants was determined by the Pearson correlation coefficient between z-transformed time series. Second, average linkage clustering was carried out based on the similarity of correlation coefficients. Termination of clustering was determined by two criteria. Two participants or cluster were aggregated into a further cluster if mean correlation among time series in the new cluster would not fall below the threshold of $r = 0.5$. This threshold was chosen to ensure that the correlation within a cluster represents a large effect with respect to the classification of effects proposed by Cohen (Cohen, 1992). Additionally, a cluster had to consist of at least four participants. This minimal cluster size was chosen so that a cluster represented at least 10% of the given sample and thus avoided the formation of clusters that represented rather individual trajectories instead of a shared response pattern. The application of these two rules led to clusters of individuals with at least four participants who showed a mean correlation of their time series of $r >= .5$. This approach is in line with current recommendations in time series analyses (Aghabozorgi et al., 2015). While it ensures that only clusters with sufficient similarity are formed, it is possible that some participants will not be part of the cluster solution. However, given the complexity of the stimuli, a finite clustering approach did not seem appropriate. To depict the identified heart rate patterns of the clusters, the mean time course for each cluster in each scene was computed.

Extent of changes in heart rate during movie and scenes

To characterize the extent of the individual change of heart rate, two different measures were calculated. The range from the lowest to the highest heart rate was calculated for every subject (HR_{Range}). This range expresses the individual scope of heart rate modulation experienced throughout the motion picture and in specific scenes. However, this measure could underestimate responses with lesser amplitude but longer-lasting modulation. For this reason, HR_{Sum} was calculated as sum of the squared heart rate changes during the movie and specific scenes (i.e. sum of squared residuals after pre-processing).

When derived from the entire movie, HR_{Range} and HR_{Sum} reflect the overall extent of psychophysiological adaptation. For a situational measure, we further aimed to study how changes in heart rate in a specific situation relate to empathy and HRV. If our assumption of

interindividual differences not only in the magnitude but also in the shape of the heart rate response pattern holds true, behavioral correlates of heart rate changes could be concealed when participants with differing patterns are analyzed jointly. In case of different response patterns, measures of HR_{Range} and HR_{Sum} can be numerically identical but reflect qualitatively disparate responses. Therefore, we focused on HR_{Range} and HR_{Sum} but decided on separate analyses for subgroups of different response patterns.

Statistical analysis of behavioral data

Statistical analyses were carried out with IBM SPSS Statistics for Macintosh V23 and two-tailed significance is reported at $p < .05$ and $p < .01$. Data were tested for normality with Shapiro-Wilk test and visualized as q-q plots. For normally distributed variables, independent sample t-tests were conducted to investigate gender differences and Pearson correlation was used to test for associations between HRV, measures of empathy and heart rate modulation during the movie. When assumptions of normality were violated, non-parametric testing was performed (Mann-Whitney U for gender comparisons and Spearman rank correlation for correlation analysis). Effect sizes are reported as Pearson's r coefficients.

6.2.3 Results

Participant characteristics

The sample consisted of 40 healthy men and women aged between 19 and 61 years. Sample characteristics and tests for gender differences are presented in table 2. Regarding health-related variables, men showed a higher BMI than women. No gender differences were found for age, years of education and MAP (all $p > .05$).

One out of 20 women reported to be in menopause, and seven out of 20 women used hormonal contraception. Due to uncertainties in women's self-reports, it was not possible to estimate subject-specific phases of the menstrual cycle with sufficient accuracy. However, large variability in days since last menstruation ($M = 10.69$, SD = 8.43) indicated varying menstrual phases.

Table 2.

Demographic Characteristics of the Study Sample Compared by Gender.

	Group			Statistics		*p*	*r*
	Whole sample (n=40)	Women (n=20)	Men (n=20)				
Demographic variables							
Age, median years (interquartile range)	32.0 (20.8)	32.0 (20.5)	32.0 (17.6)	*U* =	185.5	.694	.062
Education, mean years (SD)	14.9 (2.8)	15.3 (3.01)	14.5 (2.6)	*t*(38) =	-.923	.362	.141
BMI, median (interquartile range)	23.4 (4.7)	22.1(6.0)	24.5 (4.0)	*U* =	125.5	.044	.319
MAP, mean (SD)	93.2 (9.0)	92.7 (8.7)	93.7 (9.6)	*t*(38) =	.352	.727	.054

Note. BMI, body mass index; MAP, mean arterial pressure. Effect size is reported as Pearson r.

Do heart rate adaptations during the motion picture exceed baseline fluctuations?

The extent of a person's change in heart rate during the movie can be an initial indicator of their bodily response capacity to the emotive stimulus material. However, this capacity cannot be viewed in isolation; it must be compared to a person's heart rate fluctuations at rest. In order to demonstrate the general effect of emotional processing on one's heart rate, the range of the individual heart rate time series was calculated for the duration of the movie as well as for a five-minute resting baseline prior to the movie. The two ranges were compared with a Wilcoxon-test for non-normal data. This showed that the range during the movie was significantly larger than during baseline (Md_{Movie} = 21.69, IQR = 10.33; $Md_{Baseline}$ = 4.79, IQR = 3.08; Asymptotic Wilcoxon-test: z = -5.511, $p < 001$, $n = 40$, $r = .87$). This large group effect suggests a 4-5 times higher amplitude of heart rate modulation during the movie compared to a baseline condition across participants.

Correlation of heart rate time series over the entire movie

To begin with, we aimed to establish whether at least one or more patterns of heart rate dynamics were present. This would require similarity in the dynamics of the heart rate time series between participants. To test for interpersonal concordance of heart rate time series throughout the full movie, Pearson correlation between all participants were calculated. Mean correlation across all participants was $r_{mean} = 0.12$ ($SD = 0.14$). This corresponds to a small effect size for the correlation among the whole sample throughout the whole movie. Furthermore, the standard deviation for the whole sample indicated large differences in the extent of correlation between participants.

We tested for gender effects on the similarity of heart rate time courses by calculating the mean Pearson correlation among all men's time series and all women's time series and

compared this with a t-test for independent samples. Mean correlation among men did not differ from mean correlation among women, indicating equal concordance of heart rate time series in men and women ($M_{corr\_men} = 0.09, SD = 0.12$; $M_{corr\_women} = 0.16, SD = 0.15, t(38) = 1.55, p = .13$).

To further evaluate the magnitude of similarity between participants' heart rate time series throughout the movie, each participant was compared to the rest of the sample. This resulted in 39 Pearson correlation coefficients per participant and allowed us to quantify minimal, mean and maximal correlation for each participant with the other 39 participants. The magnitude of correlation between all 40 participants is displayed in Figure 2. Over all participants, the highest observed correlation coefficient between two participants was $r = .59$, and the highest negative correlation coefficient was $r = -.24$. Thus, some participants showed heart rate time series that were concordant with a large effect size.

Considering the small effect size when calculating the mean correlation coefficient for the whole sample, the simultaneous occurrence of highly similar and dissimilar time courses indicated that an analysis of mean sample-wise tendencies could be misleading. Thus, we tested whether there were clusters of participants with highly similar heart rate time series throughout the movie. We used the criteria that were also applied for the clustering during emotive scenes (i.e. at least four participants, mean $r > .5$). However, only one cluster of four participants with a mean cluster correlation of $r = .51$ could be formed. The mean heart rate time series of the single cluster is displayed in Figure 3. The time series of the remaining participants did not show sufficiently high correlations to form further clusters of concordant heart rate responses to the whole movie, indicating that participants showed highly different heart rate responses.

Cluster analyses of time series during emotive scenes

With regard to the previously specified clustering rules, heart rate time series over the entire movie showed too low correlations between participants to allow for clustering. To narrow the time window and range of emotive content, six scenes each containing one emotive event were selected to investigate short-term changes in heart rate. Cluster analyses for the six emotive scenes were carried out to identify groups of participants with concordant heart rate responses to the emotive content. Figure 4 displays the correlation matrices for all six scenes to illustrate the magnitude of correlations between participants. Based on these correlation coefficients, clusters were created. An overview of the number of clusters per scene and percentage of participants not included in the cluster solution is given in Table 3. For each scene, three or more clusters with at least four participants and mean intracluster correlation of r = .5 were formed. Thus, multiple response patterns were present in every scene.

One of the main goals of this paper was to explore if and to what extent interindividual differences in heart rate responses to emotive stimuli exist. Cluster analyses revealed that multiple response patterns were present for every scene, yet the possibility exists that one response pattern was predominant while the other clusters described less common response patterns. To investigate this, the proportion of participants per cluster was tested for each scene. If one or more dominant response patterns emerge from the cluster analysis, the distribution of participants between clusters should deviate significantly from an expected distribution of equally populated clusters. Chi Square tests were applied for each scene to test for a cluster with an exceedingly high or unexpectedly low number of participants. A deviation was found for scene one ("tsunami", $\chi^2(2) = 11.45, p < .01$), scene two ("rescue", $\chi^2(4) = 21.25, p < .001$), scene three (vomit, $\chi^2(4) = 15.50, p < .001$) and scene five ("victim reunion", $\chi^2(4) = 31.00, p < .001$). Thus, some response patterns in these scenes were more likely to occur than others. In two of these four scenes – "tsunami" and "victim reunion" – the largest cluster was formed by more than half of the sample, which indicates that for these scenes, highly predominant patterns of physiological responses were observable. No deviation from an equal distribution was present in scenes four and six (phone call, family reunion, all $p > .05$).

Table 3.

Number of Clusters per Scene with Percentage of Participants in Each Cluster and Percentage of Participants not Included in any Cluster.

	1) Tsunami	2) Rescue	3) Vomit	4) Phone call	5) Victim reunion	6) Family reunion
Nr. of clusters	3	4	4	3	4	3
P. per cluster (%)						
Cluster 1	57.5	45.0	37.5	32.5	55.0	37.5
Cluster 2	27.5	27.5	32.5	27.5	15.0	25.0
Cluster 3	15.0	12.5	12.5	17.5	10.0	17.5
Cluster 4	–	10.0	10.0	–	10.0	–
P. without cluster (%)	0.0	5.0	07.5	22.5	10.0	20.0

Note. Nr, Number; P, participant.

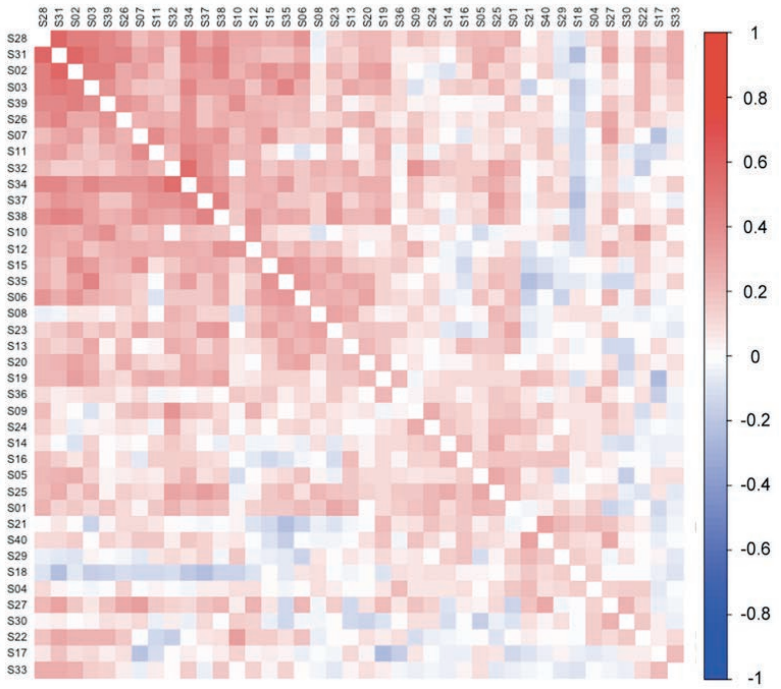

Figure 2. Overview of the Pearson correlation coefficients among heart rate time series between participants throughout the whole movie. Correlation coefficients are colour-coded from red (positive) to blue (negative) correlation coefficients.

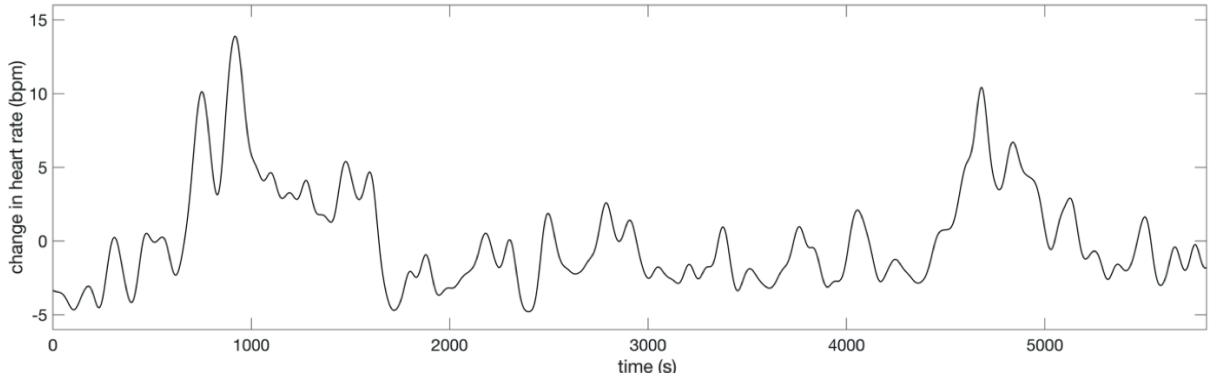

Figure 3. Heart rate time series of the single cluster formed in a cluster analysis comprising all subjects throughout the whole movie. The cluster consists of four participants. bpm, beats per minute; s, seconds

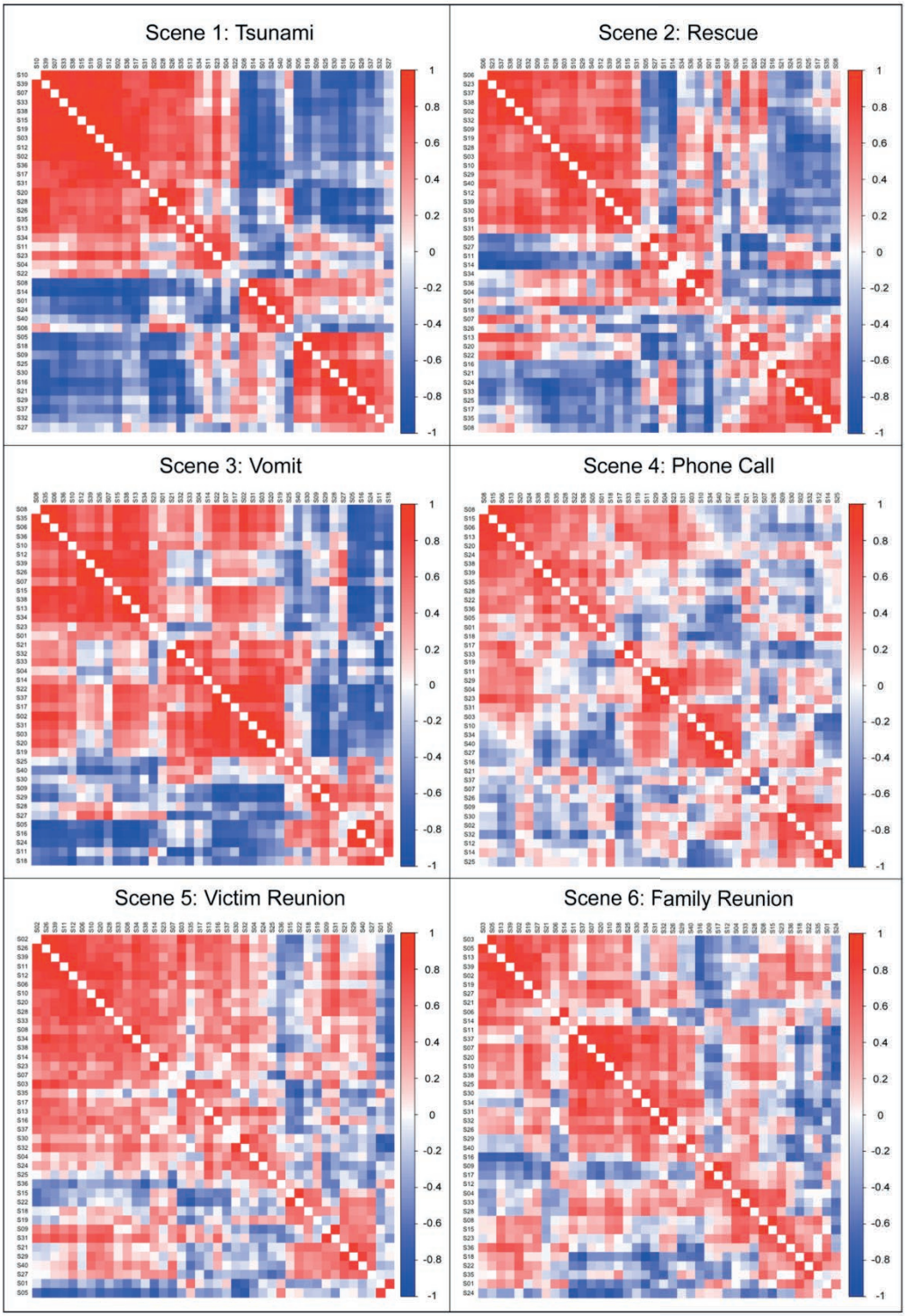

Figure 4. Correlation matrices for the six emotive scenes. Pearson correlations between the forty individual time series are displayed by colour as indicated by the colour bar. For each correlation matrix, participants were sorted in the order of the scene-specific cluster analysis results for best visibility of the clusters.

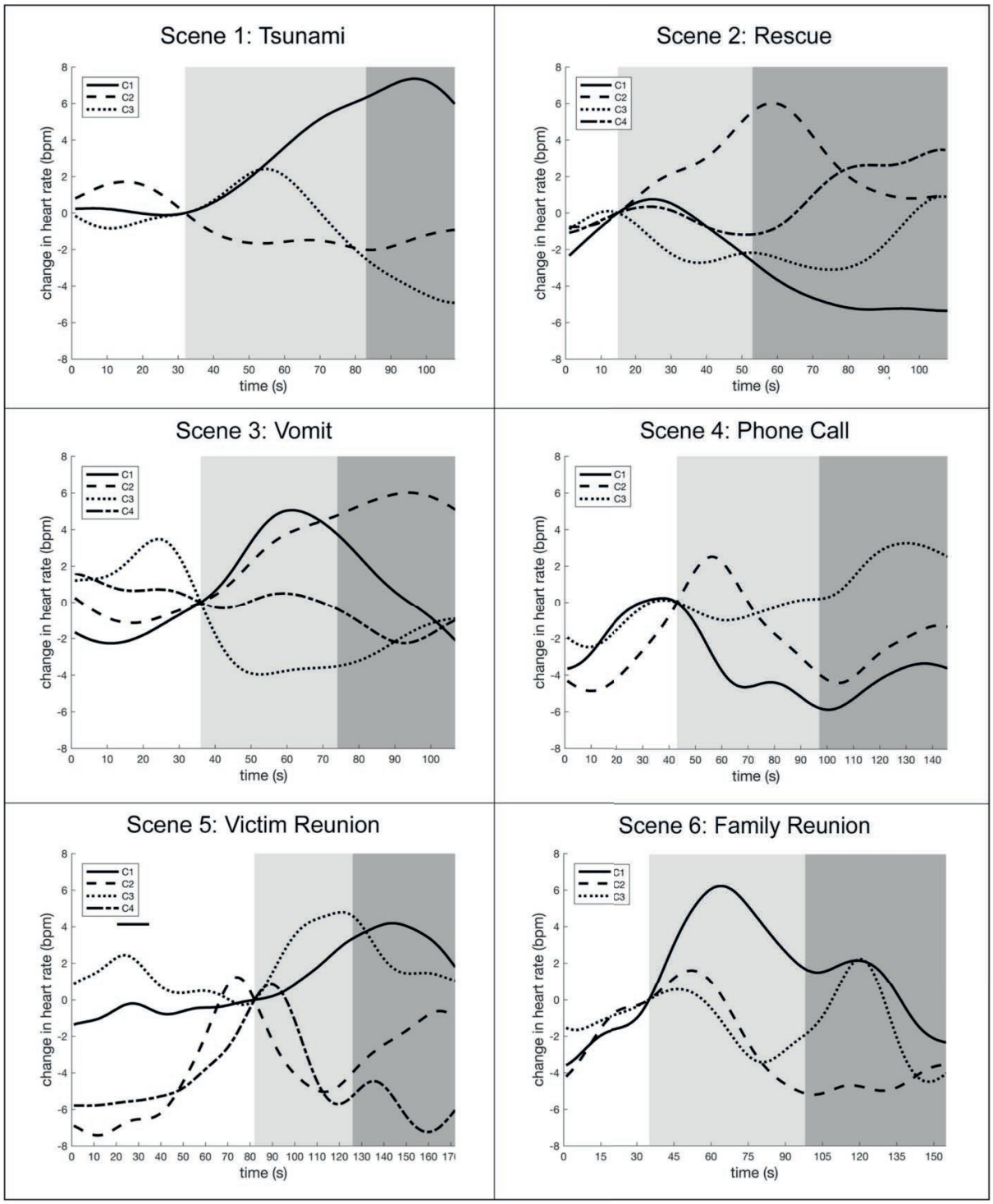

Figure 5. Illustration of mean cluster time series for the six emotive scenes. The mean time series for each cluster in each scene was calculated and plotted over the phases of the scenes. Phases were coded with the shading of the background (P1 = white, P2 = light grey, P3 = dark grey) and correspond to the progress of each scene's dramaturgy (P1 = calm phase before emotive event, P2 = immediate response to emotive event, P3 = change in intensity or emotion in the course of the scene). Time courses were shifted to zero at the onset of the emotive events to better visualize differences in the response to the emotive event.

Covariates of cluster membership

As a next step, it was of interest whether participants in one cluster differed from participants in other clusters during a scene in demographic or health-related variables. To test for differences in the distribution of men and women between clusters, Pearson Chi Square tests were conducted for each scene. For differences in age, years of education, BMI and MPA, Kruskal Wallis tests for median differences were carried out with cluster as independent samples.

Regarding gender proportion, differences were found for one scene. In scene one ("tsunami"), gender distribution differed significantly in cluster three (Fisher's exact test $z = 7.26, p < .036$) with six men but no women in this specific cluster. No further gender differences were found (all $p > .05$). There was no significant difference in the median age, years of education, BMI or MAP between clusters in any scene (all $p > .05$).

So far, we could demonstrate that large changes in heart rate were present during the perception of the motion picture, and that the trajectories of these adaptations are not uniform among participants during specific scenes. Building upon this finding, we wanted to take our analysis a step further and aim to investigate the behavioural relevance of the observed changes in heart rate. Do individuals with a stronger predisposition for empathy show larger changes in heart rate when confronted with a highly emotive motion picture? Furthermore, are those with large changes in heart rate also the ones to report intense feelings of empathy towards the motion picture's characters?

Influence of health-related variables on heart rate and heart rate variability

To rule out that the link between empathy and changes in heart rate is caused by factors related to a person's general health, we first examined the association of health-related variables with heart rate and HRV. Spearman correlations were calculated between age, BMI, MAP, RMSSD, and HR_{Range} and HR_{Sum} during the movie and tested for significance. RMSSD at rest was negatively correlated with age ($r = -.504, p < .01$) and MAP ($r = -.530, p < .01$). A negative trend was observed for the association of age and HR_{Range} during the movie ($r = -.304, p = .057$). No further significant correlations were found (all $p > .05$). To account for age and MAP, the following analyses were statistically corrected for the influence of these two variables.

Is the extent of heart rate modulation during the movie related to empathy or HRV?

We first carried out analyses on a global level and examined the association of changes in heart rate derived from the entire motion picture. Research question one targets the

association between HR_{Range}, HR_{Sum} and the self-report questionnaires on empathy. HR_{Range} showed significant positive correlations with the IRI scale empathic concern ($r = .338$, $p < .05$; see figure 6 for a visualization) and MR_{Body} ($r = .383$, $p < .05$). Additionally, HR_{Sum} was positively correlated with MR_{Body} ($r = .431$, $p < .01$). All further correlations did not reach significance ($p > .05$)

Secondly, the informative value of HRV at rest as measure of vagal tone was examined. We calculated Spearman correlation coefficients to test whether RMSSD at rest is associated with heart rate modulation during the movie and self-reported trait- and state-empathy. RMSSD at rest was not significantly correlated with HR_{Range} and HR_{Sum} as well as with the movie rating (all $p > .05$). Regarding the IRI, we found a significant correlation between RMSSD at rest and the subscale fantasy ($r = .359$, $p < .05$).

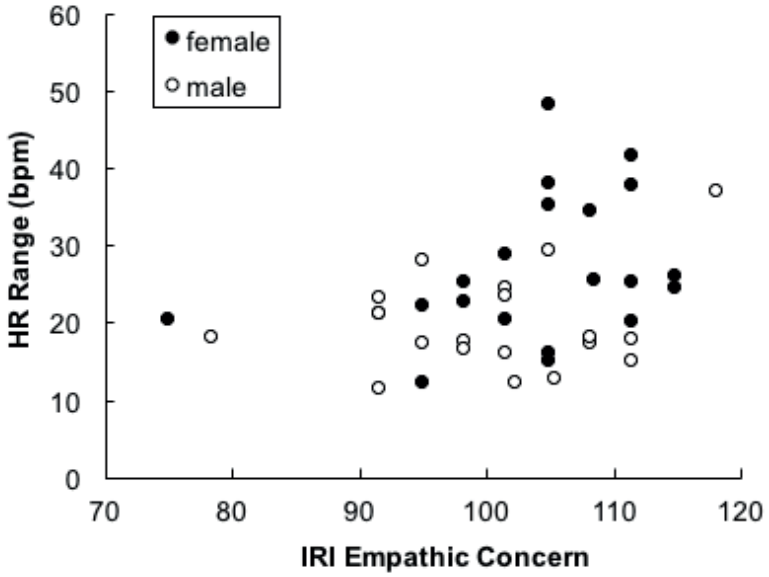

Figure 6. Scatter plot of the correlation between empathic concern measured by the IRI (Davis, 1980; Paulus, 2009) and the range of heart rate changes throughout the entire movie in women and men; bpm, beats per minute; IRI, interpersonal reactivity index

Is heart rate modulation during emotive scenes a function of empathy or HRV?

We further investigated the association of self-reported empathy, HRV and HR_{Range} and HR_{Sum} in emotionally charged scenes. Our wish was to carry out scene-specific analyses for multiple subgroups. However, this requires an adequate size of the subgroups, and many scene-specific subgroups were not large enough to allow sound statistical analyses (Field, 2009). As shown in the cluster analyses, dominant response patterns comprising of more than 50% of the study sample could be observed in two of the six scenes (i.e. "tsunami" and "victim reunion"). These two scenes were thus selected for scene-specific analyses. To test our assumption that interindividual differences in response patterns could conceal behavioral correlates, the scene-specific analyses were carried out once with the whole sample and once with the homogeneous subgroups in the two scenes.

These analyses were first carried out with focus on the homogeneous subgroups of participants showing a concordant dominant heart rate response pattern. As shown in table 4, measures of heart rate modulation during both scenes were significantly correlated with participants' movie ratings on empathy. This indicates more extensive changes in heart rate in participants who declared stronger feelings of empathy after the movie presentation. Additionally, changes in heart rate during "tsunami" were positively correlated with the IRI scales empathic concern, fantasy and personal distress. No significant correlations were found for baseline RMSSD at rest.

Note that when running the same analysis on the full sample and therefore across different response patterns, only the positive correlation between HR_{Range} during "tsunami" and IRI fantasy remained significant ($r = .357, p < .05$). In contrast to the homogeneous sub-sample, RMSSD at rest was positively correlated with HR_{Range} during "reunion" ($r = .392, p < .05$) in the whole sample. No further significant correlations were observed regarding the whole sample (all $p > .05$).

Do women and men differ in self-reported empathy, heart rate and HRV?

We tested for gender differences in self-reported empathy, RMSSD at rest and heart rate measures derived from the entire movie. As reported in table 5, women and men did not differ in RMSSD at rest. Overall, women showed a larger HR_{Range} range and higher HR_{Sum}. Because of the diversity of response patterns and consequentially small number of participants per response pattern, we refrained from testing for gender differences during specific scenes across diverse patterns.

No gender difference was found in trait empathy. However, significant gender differences were found for the movie rating that took place subsequently to the movie presentation. Women reported to like the movie better than men ($MR_{Pleasure}$), to be more emotionally touched by the movie ($MR_{Emotion}$), to feel more empathy towards the characters ($MR_{Empathy}$) and to experience stronger bodily changes as response to the movie (MR_{Body}).

Table 4.

Correlation between self-reported empathy, baseline heart rate variability and scene-specific changes in heart rate in participants showing a dominant response pattern.

	HR_{Range} tsunami	HR_{Sum} tsunami	HR_{Range} reunion	HR_{Sum} reunion
Interpersonal Reactivity Index				
EC	.458*	.379	.268	.142
PD	.335	.522*	.155	-.023
FS	.540*	.551*	-.001	-.110
PT	.097	.074	.119	. 117
Movie rating				
$MR_{Pleasure}$	.158	.050	.353	.465*
$MR_{Emotion}$	.522*	.329	.393	.451*
$MR_{Empathy}$	.455*	.402	-.021	.143
MR_{Body}	.411	.397	.467*	.405
Baseline HRV				
Baseline RMSSD	.145	.054	.432	.437
Baseline Range	.251	.053	.053	.034
Baseline Sum	.230	.052	-.004	-.016

Note. Correlations are corrected for the influence of MAP and age. EC, empathic concern; PD, personal distress; FS, fantasy; PT, perspective taking; MR, movie rating; RMSSD, root mean square successive differences; HR, heart rate; HRV, heart rate variability.

Two-tailed significance is reported at * = $p < .05$.

Table 5.

Self-reported empathy, HRV and heart rate measures compared by gender.

	Group			Statistics		*p*	*r*
	Whole sample (n=40)	Women (n=20)	Men (n=20)				
Baseline							
RMSSD, median (IQR)	35.2 (18.9)	39.1 (18.7)	34.4 (28.7)	*U* =	214.0	.705	.060
Movie							
HR_{Range}, median (IQR)	21.7 (10.3)	25.1 (14.4)	17.9 (7.3)	*U* =	294.0	.010	.436
HR_{Sum}, median (IQR)	14425.4 7289.1)	17721.6 (6726.4)	12123.0 (6468.3)	*U* =	302.0	.005	.402
Interpersonal Reactivity Index							
EC, median (IQR)	103.5 (12.6)	104.9 (12.4)	101.6 (15.0)	*U* =	259.9	.105	.256
PD, mean (SD)	95.6 (8.9)	98.1 (8.6)	93.1 (8.7)	*t*(38) =	-1.824	.076	.278
FS, mean (SD)	95.9 (8.5)	97.4 (7.9)	94.3 (8.9)	*t*(38) =	-1.183	.244	.181
PT, mean (SD)	101.1 (7.2)	100.6 (6.8)	101.6 (7.7)	*t*(38) =	.445	.659	.068
Movie rating							
$MR_{Pleasure}$, median (IQR)	73.5 (44.0)	83.0 (33.5)	54.5 (47.0)	*U* =	283.0	.025	.355
$MR_{Emotion}$, median (IQR)	87.0 (28.3)	94.5 (17.0)	73.5 (28.8)	*U* =	307.0	.004	.459
$MR_{Empathy}$, median (IQR)	88.5 (31.8)	95.5 (12.5)	76.0 (30.0)	*U* =	302.5	.005	.439
MR_{Body}, median (IQR)	71.5 (30.8)	84.0 /17.5)	57.5 (35.5)	*U* =	326.5	.001	.541

Note. Effect sizes are reported as Pearson r. EC, empathic concern; PD, personal distress; FS, fantasy; PT, perspective taking; MR, movie rating; RMSSD, root mean square successive differences; HR, heart rate; IQR, interquartile range.

6.2.4 Discussion

Capturing and characterising the temporal dynamics of emotions is an unresolved challenge. The coupling of autonomic and central nervous processes provides an opportunity to explore the psychophysiological substrate of emotions, yet the potential for interindividual diversity in psychophysiology has just recently come into the focus of social neuroscience.

In a first step of this project, we demonstrate the feasibility of a new approach to investigate interindividual concordance of heart rate responses to a highly emotive disaster motion picture. Dynamic changes throughout the movie exceeded the extent of resting heart rate fluctuations almost five times, thus qualifying our paradigm for the use in research on affective processing. We used a hierarchical agglomerative cluster analysis to distinguish patterns of heart rate responses during highly emotive scenes and could show that diversity of heart rate responses is the rule rather than the exception. Dominant response patterns observable in more than 50% of the study sample emerged in only two out of six scenes with highly imperative stimuli.

Secondly, we set out to explore the relationship of heart rate changes during the motion picture with empathy and HRV as measure of emotional flexibility (Appelhans & Luecken, 2006). As a main result, we were able to show that more extensive changes in heart rate throughout the movie were significantly associated with higher self-reported empathic concern. The behavioural relevance of discordant heart rate response patterns could be further substantiated: The link between empathy and changes in heart rate was only significant when examining homogeneous subgroups, yet it was concealed when we re-run the analysis on the full sample. Contrary to our hypothesis, vagal tone at rest quantified by RMSSD at rest was not consistently related to changes in heart rate nor empathy.

Methodological considerations

The involvement of the autonomic nervous system in emotions is undisputable, yet characterizing the autonomic responses in emotions has been an ongoing challenge. Much effort has been invested in the search for general autonomic patterns of emotional experiences, but so far studies have failed to demonstrate universal autonomic patterns for distinct emotions (Kreibig, 2010). The approach presented in this study has the potential to overcome weaknesses of previous research because it is oriented towards major characteristics of emotional experiences. The main target points are outlined below.

Many studies have attempted to characterize responses to an event by analysing the mean change in heart rate between a baseline A and a time point B at which the emotion is assumed to be present. The success of such an approach would require homogeneous interindividual autonomic responses that follow a known and invariant time course with clearly defined start and end points. However, these prerequisites are not met. To begin with, the onset of an emotion does not necessarily coincide with the beginning of the internal or external event that initiates the emotional process (Hollenstein & Lanteigne, 2014; Verduyn et al., 2015). As the emotional experience continues, interindividual differences in cognitive appraisal and emotion regulation would further increase the potential for discordant autonomic responses (Gross, 2015; Thayer & Lane, 2000). Finally, termination of an emotion is difficult to define (Verduyn et al., 2015), and depends on prior central nervous and autonomic processes (Barrett, 2016) such as the extent and mechanisms of emotion regulation (Ochsner & Gross, 2005). For all these temporal characteristics of emotions, it is not sufficient to merely compare heart rate at an assumed baseline condition and a specific time point after an emotive stimulus.

To incorporate these features of emotional processing and investigate associated autonomic changes appropriately, our approach refrained from calculating mean change scores.

Instead, a broad time window for each emotional experience was investigated. By portraying the autonomic adaptation during different phases before, during and after the emotive event, onset and dynamics of changes in heart rate become visible. This enabled us to observe temporal characteristics of the autonomic changes as emotions emerge and unfold throughout scenes.

Temporal characteristics could help to differentiate between emotional response types. Scene five serves as an example in this regard. During this scene, Lucas helps a father to find his son and the two are reunited. While participants in cluster two and four showed a large increase right before or shortly after the beginning of the emotive event (i.e. Lucas detects the lost son), participants in cluster one and three showed the largest changes in heart rate later during phases two and three (i.e. Lucas reunites father and son; they share an intense hug). This points to the influence of anticipation for emotional experiencing (Barrett, 2016; Baumeister, Vohs, Nathan DeWall, & Liqing Zhang, 2007). It is possible that participants in cluster two and four anticipated the following events and thus showed early heart rate changes, whereas participants in the other clusters did not react before the actual emotive action occurred. Additionally, the respective two clusters with similar time series appear to be shifted slightly in time. The general tendency of an increased heart rate either during anticipation of a reunion or while watching the reunion of father and son are in line with previous findings regarding joy and relief, which are commonly associated with an accelerated heart rate (Kreibig, 2010).

The second premise concerns the homogeneity of autonomic adaptations during emotional experiences between individuals. The frequently applied approach of testing individually calculated change scores at a group level would only be able to detect significant autonomic changes if participants show highly similar responses. Considering the importance of conscious and subconscious processes of perception, evaluation and appraisal in emotional experience (Barrett, 2016; Brosch, Pourtois, & Sander, 2010), it seems improbable to assume homogeneous adaptations given the vast number of possible interpretations of a stimulus.

A few recent studies have addressed the question of interindividual homogeneity of bodily responses to emotive stimuli. Golland and colleagues (2014) presented a 36-minute excerpt of a movie to participants and recorded changes in heart rate and electrodermal activity. Heart rate time series showed an interindividual correlation of medium effect size when the full excerpt was analysed. Furthermore, correlation between participants varied considerably throughout the movie. In a second study (Golland et al., 2015), shorter movie clips of approx. 10 minutes were presented; however, only correlations of small effect sizes were observed. Albeit the emotive material in this study is much shorter than in their previous work (Golland et al., 2014), they reported lower interindividual correlations. This implies that the extent of

interindividual similarity in autonomic responses is not solely determined by the length of the emotive material presented. Not only movies but also storytelling has been used to investigate emotionally driven changes in heart rate. Wallentin et al. (2011) presented the narration of a children's story to adult participants and were able to show dynamic adaptation of heart rate variability that correlated with continuous ratings of valence and arousal of the story. So far, these studies demonstrated that autonomic signals show some degree of homogeneity among individuals. Our results support these findings, and by applying cluster analyses we were able to show striking correlations of heart rate dynamics for subgroups of participants that would have been hidden if all participants had been examined altogether to find a general response.

Determinants of emotional experiences

This first part of this study served to explore the variety of autonomic response patterns to emotive stimuli and challenged the premise of homogeneous and time invariant responses during emotional experiences. We observed predominant response patterns for scenes containing very strong, imperative stimuli such as the dreadful tsunami and a dramatic family reunion. In these two scenes, over half of our study sample showed highly similar heart rate response patterns. This is impressive given the richness of the stimulus material including numerous individuals and thus identification figures, sounds, music, voices and impressions from previous parts of the movie plot, as well as interindividual differences in the cognitive appraisal of stimuli. However, such extensive interindividual concordance was only present for two scenes. Thus, the main finding and most important benefit of the presented approach is the diversity of heart rate response patterns to pseudo-naturalistic emotive scenes. Since most studies have not considered discordant bodily responses to emotive stimuli, it is crucial to understand how various patterns can emerge from identical stimuli.

Bodily adaptations depend on the perceived relevance of a stimulus for the individual in a specific situation (Hamm, Cuthbert, Globisch, & Vaitl, 1997; Smith et al., 2017). In our study, participants were aware of the artificial situation and knew that emotions are evoked by their perception of the movie. Thus, the initial relevance of the presented movie is fairly low. However, relevance of the movie content can increase drastically if a participant becomes involved in the story. The scope of bodily changes could reflect a function of how much participants identify with actors and how deeply they feel involved in the plot.

Relevance itself is not sufficient to determine one's emotional experience and associated bodily adaptations. Although many studies hold this assumption at least implicitly, it should be considered that presented emotions do not necessarily correspond to the evoked emotions

(Brosch et al., 2010). This is a frequent problem in passive viewing paradigms where one person (the stimulus) displays an emotional expression and the emotional experience of another person (the participant) is measured. An angry face probably does not induce anger in the observer, but rather fear, discomfort or plain confusion if no reason for anger is apparent. Watching another person cry might elicit sadness, yet also reactions of frustration, distress or – when the cause of the tears is judged as ridiculous – even contempt are possible. It becomes apparent that much of what we experience depends on how we appraise our environment (Brosch & Sander, 2013). Appraisal of situations relies, among other processes, on the social-cognitive functions that we use to infer emotions, thoughts, beliefs and intentions from interaction partners (Mitchell & Phillips, 2015). In social situations, there is no correct objective definition, but rather each person constructs a subjective inner representation of the social surrounding to imbue the social world with meaning. The efficiency and accuracy with which we infer social information is shaped by our previous experiences and determines how we perceive the situation at hand (Fiske & Taylor, 2013). This highly individual interpretation is one of the determinants for emotional experiences and likely leads to the multitude of possible autonomic adaptations. An example for this can be deduced from scene three. In this scene, Lucas offers a piece of clementine to an unknown woman (P1), who starts to throw up blood and undefined bloody mass (P2), and shortly after his mother starts to throw up as well (P3). If one pays more attention to the act of throwing up, this probably induces changes related to disgust from contamination, which would result in an increase in heart rate (Kreibig, 2010). On the contrary, a focus on the potential for bodily harm and the mass that Maria tugs out of her throat, disgust is induced by observed bodily mutilation and which conceptually translates to a decrease of heart rate (Critchley et al., 2013). This example shows how already small changes in one's spotlight of attention can produce different autonomic adaptations. Of course, it remains speculative to what extent participants have interpreted the scene accordingly.

In conclusion, the wealth of intrapersonal and environmental determinants of emotional processing calls for measures that allow us to differentiate between a multitude of possible responses. To date, many inconsistencies in the research of the physiological correlates of emotions have emerged (Kreibig, 2010). These could be the consequence of analytic tools that have not been optimally adapted to capture the evoked signals during emotions. We believe it is essential to tailor the methodological approach to the signal of interest. The approach presented in this study offers a more nuanced look at the variety of physical responses associated with emotional experiences. We suspect that participants with highly similar response patterns also hold similarities in the many determinants of emotional experiences,

such as their perception and interpretation of emotional signs portrayed by the actors. Based on current knowledge about the interplay of mental and bodily processes in emotional experiences, we assume that participants with concordant bodily responses share whole-body experience of emotion.

Significance of empathy for psychophysiological adaptation

In addition to offering an innovative approach to study the psychophysiological correlates of emotions, this study is among the first to show a link between changes in heart rate and the tendency to empathize with others during the perception of social situations. In agreement with our findings, Oliveira et a. (2011) showed an association between levels of empathy and changes in heart rate. In contrast to the current study, participants had to formulate a hypothetical response to short emotional film clips. Thus, their task requires active involvement of the participant, while our study setting was based on passive viewing of the motion picture. Truzzi et al. (2016) showed that regardless of the context of a perceived social interaction, those with higher empathy and lower levels of autistic traits showed larger changes in heart rate. This implies that the association of heart rate with empathy can be found across different approaches and with a variety of stimuli conveying social information. Possibly, these findings reflect a general tendency of individuals with more pronounced empathy to show larger psychophysiological adaptations as response to social interactions.

Our study offers new approaches towards empathy on two levels. First, the presentation of an entire motion picture meets the demand for lifelike study designs (Schilbach et al., 2013; Zaki & Ochsner, 2012) and provides a multitude of opportunities to share the affective state of the characters on screen. Secondly, our findings highlight the usefulness of psychophysiological recordings. Traditional measures of empathy such as questionnaires have often been criticized for their little validity (Melchers, Montag, Markett, & Reuter, 2015), yet they gain in meaning when combined with additional measures such as psychophysiology.

A further novelty of the current study is the analysis of subgroups defined by their heart rate response pattern during selected scenes. Studies on the similarity of psychophysiological responses to emotionally charged material have shown little correlation of changes heart rate in general (e.g. Golland et al. 2014). Our findings go a step further by showing that this low correlation actually arises from qualitatively different response patterns. We thus believe that it is more appropriate to divide samples based on participants' psychophysiological responses and subsequently examine behavioral correlates like empathy in homogeneous subgroups. In accordance with this rationale, we found significant correlations between changes in heart rate

and self-reported empathy during two selected scenes. Interestingly, these associations were not observed when re-running the analysis on the whole sample. This reinforces the necessity of analyses that have the potential to reveal interindividual differences not only on the behavioral but also on the psychophysiological level. Although it was not possible to investigate the relationship between empathy and all the observed response patterns during scenes, these first findings for the dominant response pattern point out that differential response patterns carry behavioral relevance.

Gender differences in empathy and psychophysiological adaptation

Women and men showed considerable differences in our study. Women not only reported more feelings of empathy throughout the movie, their actual changes in HR exceeded those in men significantly. However, all participants watched the movie in the presence of a female staff member, thus gender-related experimenter effects and interactions with the social situation have to be considered (Horgan & Smith, 2006). Possibly, men engaged more in strategies of emotion regulation to avoid being perceived as "too emotional" or "weak", whereas women could have felt social pressure to produce more intensive emotional responses. Nevertheless, all these effects also occur in our daily lives, and avoiding them could distort the actual phenomenon. Contradictory to our findings, previous studies (e.g. Codispoti et al., 2008) reported no gender effect on HR as response to emotional film clips. Therefore, it is still unclear to what extent frequently proclaimed fundamental phylogenetic and ontogenetic gender differences in empathy (Christov-Moore et al., 2014) actually prevail.

Is heart rate variability at rest indicative of empathy?

We further addressed the informative value of HRV at rest as possible index of emotional and autonomic flexibility (Thayer et al., 2009). This assumption was fostered by findings of Quintana et al. (2012) who showed that individuals with high HRV were more accurate in the understanding of other's mental and affective states. In conflict with this current interpretation of HRV, we did not find the expected link between HRV and empathy or changes in heart rate. This discrepancy could be caused by the choice of HRV parameter. To rule out this possibility, we re-run the analysis with resting HF-power in the frequency domain as well as HR_{Range} and HR_{Sum} derived from the baseline instead of RMSSD, but results did not change. Consistent with our results, Tracy and Giummarra (2017) did not find any association between RMSSD and empathy in men and even an inverse relationship in women. So far, the behavioral relevance of resting HRV remains ambiguous. Lately, it was put forward that not vagal tone

but vagal flexibility, defined as greater cardiac vagal withdrawal during tasks, could serve as an index of social sensitivity (Muhtadie et al., 2015). However, such a comparison between resting and task states requires an equal length of analysed time windows and continuous demands during windows (Task Force of the European Society of Cardiology, 1996). Given the complexity and temporal dynamics of our stimuli, this is not feasible in our study design. Therefore, future studies with designs tailored to this question are necessary to address this proposal.

Clinical implications

Alterations in emotional as well as autonomic processes are features of many pathologies such as epilepsy (Broicher, Frings, et al., 2012; Lotufo, Valiengo, Benseñor, & Brunoni, 2012), traumatic brain injuries (Francis, Fisher, Rushby, & McDonald, 2016), anxiety disorders (Friedman, 2007) or schizophrenia (Hempel et al., 2005). However, the assessment of a patient's daily emotional functioning poses a challenge for clinicians. It is frequently criticized that current testing procedures aimed at measuring associated functions such as emotion recognition or empathy are lacking in ecological validity (Risko, Laidlaw, Freeth, Foulsham, & Kingstone, 2012). Patients often find themselves in the roles of passive observers while processing stimuli of little relevance to their lives (Schilbach et al., 2013), which impedes research on authentic emotional experiences. In the paradigm we chose, the presented movie addressed easily accessible themes, thus setting a stage for the socio-cognitive functions of the spectator. Still, the participant remains in the position of an observer, yet processes of relevance and identification are facilitated. This allows us to study physiological emotional signals while participants are at least partly engaged in the situation they are perceiving.

Furthermore, many patients probably suffer from rather subtle impairments in emotional processing that can easily be overlooked in group analyses (Bonora et al., 2011). By analysing the time course of heart rate and the degree of similarity to neurotypical patterns, it may be possible to detect responses with pathological relevance in clinical samples characterised by neurological and psychiatric diseases.

Limitations

The presented approach offers many possibilities, but it also comes with new challenges. For a start, the richness of a movie as stimulus material leads to numerous ways of appraisal and interpretation. Although the content presented can be described thoroughly, the individual emotional experience remains unknown. It is possible that the clusters identified during emotive

scenes correspond to varying shades of the same emotion or even entirely different emotions. One could try to put a label on the perceived emotion via subsequent self-report of participants, yet often language fails to capture emotional experience (Cacioppo et al., 2000), and self-reports could interrupt the emotional experience itself. However, even in case the changes in heart rate do not fully correspond to shared affective states, they are still a reaction to the social situation on screen and are related to self-reported empathy in their extent.

Additionally, it is also possible that some clusters consisted of individuals who show little heart rate change associated with emotions but are similar in other physiological processes. For this reason, an interpretation of clusters and their response patterns requires close attention to the experimental setting and the recorded physiological signals. However, cluster analysis is a powerful tool to generate clinically meaningful results such as dissimilar responses in clinical groups in the future, which then need further interpretation within the specific paradigm.

While all of the participants watched the motion picture in the presence of a staff member, six participants attended the study in pairs for the benefit of optimal resource utilization. A previous study by Golland and colleagues (2015) reported that concordance of psychophysiological signals was slightly higher between confidante individuals who watched a movie together compared to strangers who attended another session of the experiment. Golland et al. (2015) attribute this effect to synchronization based on emotional signals provided by the confidante, that would lead to more synchronous affective states. However, it is not clear whether these differences arose in the presence or absence of a staff member. In our study, all participants watched the motion picture while a staff member stayed with them in the room. This limited their possibility to express emotional signals such as sounds or exchange views. We acknowledge that the presence of a confidante person can have an influence on one's emotional experience, yet we believe the effect in our data is minimized due to the presence of the staff member.

Finally, the heart is innervated by both branches of the autonomic nervous system. Thus, parasympathetic as well as sympathetic influences are reflected in heart rate recordings (Palma & Benarroch, 2014). Attempts have been made to disentangle the two subsystems by measuring frequency-domain measures, yet this remains controversial (Billman et al., 2015). Additionally, some frequency domain measures require recordings of at least five minutes duration (Task Force of the European Society of Cardiology, 1996), thus the dynamics in emotional processing cannot adequately be captured. To us, a more promising approach is one that combines measures of heart rate with further autonomic signals such as electrodermal activity as used by Golland et al. (2014).

Conclusion

In this feasibility study, we addressed the challenge of measuring autonomic adaptations during emotional processing and proposed an approach based on cluster analyses of heart rate time series. To our knowledge, this is the first study in which heart rate during a full motion picture was individually analysed. This allowed us to create an immersive, pseudo-naturalistic and easily accessible emotional experience. We were able to demonstrate that a variety of heart rate responses to emotive scenes are the rule rather than the exception. Therefore, we encourage the use of cluster analyses on autonomic signals in order to unravel changes in autonomic and emotional processes. Our results indicate that the complexity of human emotional processing translates to diversity on the psychophysiological level.

Furthermore, our study is among the first to show that the tendency to empathize with others is reflected by the extent of changes in heart rate during the processing of social situations. Our findings contribute to a deeper understanding of empathy and emphasize the importance of interindividual differences in research on psychophysiological correlates of individual predispositions. Empathy may manifest itself in the readiness to mirror the psychophysiological state of others. Its relevance can easily be overlooked if interindividual differences in psychophysiological processes are not taken into account. However, when making room for interindividual similarity and diversity in autonomic adaptations, empathy possibly serves as a magnifying glass for social signals.

Supplementary table 1.

Correlation between Mean Heart Rate Time Series of Clusters within Each of the Six Emotive Scenes.

	C1	C2	C3
Scene 1: tsunami			
C1	–		
C2	-.739**	–	
C3	-.637**	.072	–
Scene 2: rescue			
C1	–		
C2	-.142	–	
C3	.076	-.700**	–
C4	-.702**	-.370**	.259**
Scene 3: vomit			
C1	–		
C2	.496**	–	
C3	-.862**	-.732**	–
C4	-.095	-.809**	.431**
Scene 4: phone call			
C1	–		
C2	.360**	–	
C3	.496**	-.372**	–
C4	-.309**	.354**	-.152*
Scene 5: victim reunion			
C1	–		
C2	-.142	–	
C3	.076	-.700**	–
C4	-.702**	-.370**	.259**
Scene 6: family reunion			
C1	–		
C2	.287**	–	
C3	.194*	.263**	–

* = $p < .05$. ** = $p < .01$

7 General discussion

Motivated by the ubiquity and centrality of social interactions in our daily lives as well as the immense clinical relevance of socio-cognitive functions, the overarching goal of this thesis was to investigate core processes of social cognition in a multimodal approach. By use of latest techniques in neuroimaging and psychophysiology, this thesis aspired to explore the neural and bodily circuits underlying emotion perception and empathy in innovative and life-like study designs. In the following general discussion, the main findings of the theoretical study and the two empirical studies presented in this thesis are summarized. Subsequently, theoretical as well as clinical implications of this thesis' findings are discussed. Based on the presented findings, limitations and consequentially future directions for research are elaborated. Finally, the thesis closes with concluding remarks.

In the theoretical study preceding the empirical part, socio-cognitive deficits were identified as substantial threat for the social integration of people with MTLE. Affected individuals can find themselves challenged by deficits in basal socio-cognitive functions of emotion perception (Monti & Meletti, 2015) and are furthermore at risk for being less efficient in the inference of mental and affective states of others (Bora & Meletti, 2016; Broicher, Kuchukhidze, et al., 2012; Stewart et al., 2016). Whether these socio-cognitive impairments are the cause or rather the consequence of social disintegration and disease-related stigmatisation of people with epilepsy cannot be deduced from current research with certainty (Jacoby et al., 2005). At least, deficits can already be found in children with MTLE (Golouboff et al., 2005), thus hinting at an early disruption of socio-cognitive functions in affected individuals. In addition, psychiatric comorbidities (Quintas et al., 2012) and further neuropsychological deficits (Jokeit & Steiger, 2016; Stretton et al., 2012), which are frequently found in people with MTLE, can impede smooth social encounters. Currently available diagnostic tools (Henry et al., 2016) do not live up to the wealth of information provided by the complex social environment we live in. This gap between the contemporary diagnostic practice and the demands of real-life social interactions needs to be addressed to obtain a better understanding of social cognition and to integrate this domain into comprehensive neuropsychological assessments. The two empirical studies of this thesis strived to reduce this gap.

The first empirical study set out to investigate the intrinsic functional network underlying the perception of facial emotional expressions in individuals with MTLE. In this clinical population, widespread alterations in brain activity during the perception of facial emotional expressions have been shown repeatedly (Labudda et al., 2014; Schacher,

Haemmerle, et al., 2006; Toller et al., 2015). Additionally, a growing body of studies indicates that intrinsic functional brain networks are disrupted in MTLE (Cataldi, Avoli, & de Villers-Sidani, 2013). However, the intrinsic FC among regions involved in the perception of facial emotional expressions has not been studied so far and thus formed the objective of the first empirical study. In a first step, crucial regions were inferred by presenting dynamic fearful faces and dynamic landscapes in a block-design fMRI paradigm (Schacher, Haemmerle, et al., 2006) to healthy participants. Peak activations determined the ROIs for the subsequent analysis of intrinsic FC, which was carried out in a second group of healthy controls, participants with extratemporal seizure onset and groups of participants with left- and right-sided MTLE. Although data was collected during the same behavioural paradigm, the regression of task-related changes in the BOLD signal allowed for the analysis of intrinsic FC (Cole et al., 2014; Smith et al., 2009). In healthy participants, a widespread and highly interconnected intrinsic functional network encompassing both amygdalae as well as frontal, temporal and insular cortices and the PAG could be observed. In contrast, extensive network alterations were present in both left- and right-sided MTLE. While a narrowed network involving the right amygdala as well as frontal and temporal ROIs was found in left-sided MTLE, participants with right-sided MTLE showed almost no significant FC among the investigated ROIs. Regardless of the hemisphere of seizure onset, MTLE was associated with functional disruptions among the amygdala, anterior insula and pSTS. Influences of AEDs or unspecific factors related to epilepsy cannot explain these alterations for participants with extratemporal seizure onset still showed an extensive functional network. Additionally, we found little influence on the participant's age and the duration of epilepsy. Therefore, research question one can be answered as such that extensive alterations of the intrinsic functional network involved in the processing of facial emotional expression are presented in left- and right-sided MTLE, but are far more accentuated in right-sided MTLE.

The second empirical study draws upon the wealth of research which demonstrates that psychophysiological adaptations are a central component of emotions (Cacioppo et al., 2000; Kreibig, 2010; Stemmler, 2004). Although general tendencies regarding the changes in heart rate during basic emotions have been reported (Kreibig, 2010), it has yet to be investigated to what extent these adaptations vary among individuals when faced with complex social stimuli. A potential source for interindividual differences is the individual tendency to empathize with others. Empathy as a key influence factor in social interactions describes a person's tendency to share the affective – and thus also bodily – state of another person (Critchley et al., 2013; de Vignemont & Singer, 2006), yet few studies have investigated the role of empathy in

psychophysiological adaptations to emotive stimuli. To bridge these gaps, the second empirical study aimed at a new methodological approach to capture the temporal dynamics and interindividual differences of changes in heart rate during emotional experiences. Additionally, this study served to investigate the association between changes in heart rate, self-reported empathy and HRV, which is currently discussed as measure of autonomic flexibility (Appelhans & Luecken, 2006). To meet these aims and to evoke emotions as life-like as possible, we presented the disaster motion picture "The Impossible" (Hermida Muniz et al., 2012) to 40 healthy adult participants and recorded their heart rate throughout the motion picture. Analyses of heart rate were selected with respect of the heart's capacity for fast as well as sustaining adaptations during emotional processing (Critchley & Harrison, 2013; Task Force of the European Society of Cardiology, 1996). In a first step, agglomerative hierarchical cluster analyses were applied to explore the diversity of heart rate response patterns during the entire motion picture and six emotionally charged scenes. Dominant response patterns encompassing the majority of participants were found in two out of six scenes. For the remaining scenes, we found that changes in heart rate were not uniform but could rather be aggregated into several subgroups. Secondly, we explored the association between changes in heart rate, self-reported empathy and HRV by means of correlation analyses. On a global level, higher self-reported empathy was significantly correlated with more extensive changes in heart rate throughout the motion picture. In scene-specific analyses, this link could only be replicated when subgroups of homogeneous heart rate trajectories were examined, but was concealed when testing the correlation across all participants and thus response patterns. As an exploratory finding, women showed both larger changes in heart rate as well as stronger self-reported feelings of state but not trait empathy. Contrary to our hypotheses, we failed to find a significant association of HRV at rest with either empathy or changes in heart rate.

7.1 Theoretical implications

7.1.1. Emotion perception from a network perspective

The process of facial emotion perception is a building block for social interactions (Jack & Schyns, 2015) and constitutes one key topic of this thesis. The first empirical study served to investigate intrinsic FC among regions involved in this process and examined network disruptions in the context of MTLE. A vital step for this study was the determination of ROIs among which intrinsic FC was calculated in the four groups. ROIs were selected based on the application of the well validated paradigm first presented by Schacher and colleagues (Schacher, Haemmerle, et al., 2006), which allows to contrast brain activation in response to

dynamic fearful faces and dynamic landscapes. This paradigm enabled us to identify regions involved in the processing of naturalistic, dynamic faces displaying intense fear. In order to maximize signal from the mesial temporal lobe, an fMRI sequence covering frontal, temporal and partly parietal lobes was used, thus impeding any conclusion regarding occipital face processing areas. The temporal and frontal activation found in healthy participants closely corresponded to the areas subsumed in the dorsal stream of face processing in the framework of Duchaine and Yovel (2015). In line with latest meta-analyses focusing on the additionally recruited brain regions in the context of emotional facial expressions (Fusar-Poli et al., 2009; Lindquist et al., 2012; Sabatinelli et al., 2011), our paradigm further evoked activation in the amygdala and the anterior insula. This replication of current models and meta-analytic findings supports the selection of ROIs for the subsequent analysis of FC.

The analysis of intrinsic FC builds upon the discovery of intrinsic functional networks that are assumed to represent the brain's inherent functional architecture (Buckner et al., 2013, Cole et al., 2014). Previous research has shown that the amygdala, which is central to the detection of salient and behaviourally relevant stimuli (Adolphs, 2010; Pessoa & McMenamin, 2017), is part of extensive functional networks related to emotion perception and empathy (Bickart et al., 2014; Stanley & Adolphs, 2013). In our healthy control group, we could replicate the extensive functional connections of the amygdala to frontal, temporal, insular and brainstem regions and further showed connections among these regions related to face processing as well.

In line with the assumption that the amygdala is involved in the allocation of processing resources (Pessoa & Adolphs, 2010), previous studies have shown a modulatory influence of amygdala activation during emotion perception on basal and superior temporal areas (Foley et al., 2012; Furl et al., 2013). In the current thesis, the modulatory role of the amygdala can be inferred from the network alterations observed in the two groups of participants with MTLE. Previous analyses on task-related activity during facial emotion perception already indicated lesser recruitment of the afflicted amygdala but also further distributed brain regions in MTLE (Labudda et al., 2014; Schacher, Haemmerle, et al., 2006; Toller et al., 2015). Additionally, FC during facial emotion perception showed lateralized alterations in individuals with MTLE (Broicher, Frings, et al., 2012). By analysing intrinsic FC among crucial brain regions in the first empirical study of this thesis, it became apparent that the loss of functional integrity of the amygdala has widespread consequences for the investigated functional network. Not only was the afflicted amygdala functionally de-coupled from the other ROIs, but network alterations were also observable among the remaining regions, hinting at less efficient processing of information in the presence of MTLE (van den Heuvel & Hulshoff Pol, 2010). This supports

the assumption that the integrity of the functional network underlying the perception of facial emotional expressions heavily rests on amygdala functions (Pessoa & Adolphs, 2010).

Although the first empirical study examined intrinsic and not task-evoked FC related to the processing of facial emotional expressions, the deduction of ROIs is influenced by the emotional expression that was presented. Notably, ROIs were determined by use of a paradigm that depicts dynamic fearful faces and dynamic landscapes. Whether findings from this study can be generalized to other emotional expressions such as anger or joy must be considered with caution. Latest meta-analyses (Fusar-Poli et al., 2009; Lindquist et al., 2012; Sabatinelli et al., 2011) led to the conclusion that the perception and recognition of facial emotional expressions does not require disparate neural circuits for each emotion category, but rather indicate a more general set of brain regions involved in emotion perception (Barrett & Satpute, 2013; Touroutoglou et al., 2015). This raises confidence that findings of the first empirical study can serve as a reference for future work not only on the processing of fearful expressions but in emotion perception in general.

7.1.2 How analysing changes in heart rate can enhance our understanding of emotions and empathy

Emotion perception is a crucial process in order to infer the affective and mental states of others, yet it should not be interpreted in isolation. Moreover, social cognition needs to be understood as a continuous and dynamic process during which one perceives social signals and utilizes the deduced information in order to adapt oneself to the demands of the current situation (Appelhans & Luecken, 2006; Frith & Frith, 2012; Mitchell & Phillips, 2015). This adaptation involves the alteration of bodily states via the SNS and PNS, which convey top-down modulatory influences of the CAN to target organs (Benarroch, 1993; Thayer & Lane, 2000). The second empirical study of this thesis takes advantage of the heart's dual innervation by both branches of the ANS and its potential for quick and long-lasting adaptations (Palma & Benarroch, 2014) and used measures of heart rate to investigate the bodily component of emotions. While the study aims at the potential for diversity of heart rate responses during emotional experiences, it must first be discussed whether the paradigm of choice was suitable for the study's purposes.

Previous research predominately applied emotive pictures, short film clips, imagination tasks or behavioural designs such as the preparation of a speech or the anticipation of stimuli (e.g. electric shocks) in order to induce emotions in participants (Kreibig, 2010). Studies using more extensive paradigms at best lasted up to 40 minutes (e.g. Golland et al, 2014; Wallentin

et al., 2011). Thus, the application of an entire motion picture is a novelty in the field of psychophysiology, and its suitability has to be evaluated. Analyses of changes in heart rate across the entire motion picture showed that in comparison to a resting baseline condition, participants' range of heart rate exceeded the range at rest almost 5 times, therefore indicating large changes in heart rate during the perception of the motion picture. Furthermore, the analysis of specific emotive scenes, which covered the main turning points of the plot, demonstrated systematic changes in heart rate during all stages of the motion picture. When questioned after the motion picture, participants reported high levels of pleasure, emotional involvement, feelings of empathy and subjective experiences of bodily reactions. The high variability of the heart rate time series throughout the motion picture combined with participants' self-report on their impression regarding their subjective experiences leads to the conclusion that the presentation of an entire motion picture is a suitable tool to investigate long-term dynamics of psychophysiological processes. As a trade-off of the long-lasting paradigm, this study design makes room for non-emotional fluctuations in heart rate, for a large proportion of the observed changes possibly stem from other processes such as metabolism or motion (Levenson, 2014). This is especially important for short phases with few emotive stimuli and points out the importance of the selection of phases or scenes of interest. With these caveats in mind, an entire motion picture proved to be a useful tool in the investigation of changes in heart rate during emotional experiences.

A key goal of the second empirical study was to investigate heart rate responses to emotive scenes and to clarify whether these responses are homogeneous among participants or if different response patterns emerged. When analysing the entire motion picture but also during specific emotive scenes, heart rate trajectories showed low mean correlation between participants, thus indicating heterogeneity of heart rate responses. By use of a cluster analytic approach, different response patterns could be demonstrated during specific scenes. Optimally, this finding would be compared to previous studies on this subject. The stimulation during emotive scenes – although embedded in an entire motion picture – would bear sufficient similarities regarding duration and complexity with film clips applied in previous research to allow comparisons. However, such a comparison is hardly possible due to the lack of studies making room for the temporal dynamics and interindividual variability of responses in their analyses. For a start, most studies rely on the common approach to compare participants' average heart rate during an emotive film clip to a resting baseline or a neutral film clip (Kreibig, 2010). This approach neglects both the temporal dynamics and the potential for diversity of responses. As a result, such studies often report only small changes in heart rate

that are not larger than 3 bpm on the group level (Balconi & Bortolotti, 2012; Codispoti et al., 2008; Palomba, Sarlo, Angrilli, Mini, & Stegagno, 2000; Truzzi et al., 2016). In the second empirical study of this thesis, changes in heart rate up to 8 bpm were observable in the course of emotive scenes, yet only when subgroups of different response pattern were distinguished first. This points out the additional informative value of our cluster-analytic procedure. If it was not for the separation of the sample into subgroups, these alterations would have been hidden. Time lag between heart rate trajectories of subgroups and even negative correlations of large effects sizes were observed, which have the potential to level out any systematic changes in heart rate on the group level. This levelling out of interindividual differences in psychophysiological responding most probably explains the findings of Golland et al. (2014, 2015), who investigated the interindividual similarity of heart rate responses to film clips. In their analysis, they did not consider disparate response patterns, and the mean correlation among participants' heart rate trajectories is comparable to whole-sample findings in this thesis's second empirical study, indicating the potential for subgroups in their data as well.

These methodological considerations highlight the need for innovative approaches which respect and make room for interindividual differences in psychophysiological responses to complex social stimuli. It is important that the potential for diversity is as broadly recognized as it is on the behavioural level. We would not expect a uniform behavioural response to an emotive stimulus; therefore, such homogeneity should not be assumed on the psychophysiological level either.

The second empirical study takes advantage of the dynamic interplay of the CNS and ANS which enables the continuous adaptation of the bodily state to the external environment and individual needs and goals (Thayer & Lane, 2000). Many studies implicitly rely on the premise that the presentation of emotive material, such as facial emotional expression of conspecifics, automatically evokes emotions in the observer without further addressing the question how the affective state and its psychophysiological component are shaped by characteristics of the observer. In the second empirical study, empathy was discussed as key motivator in social interactions with the potential to play a central role in psychophysiological adaptations when witnessing emotive content, and more specifically, social interactions and scenes. From a theoretical point of view, an association of empathy and psychophysiological adaptations arises from the definition of empathy as sharing of affective states of others (de Vignemont & Singer, 2006) and the identification of physiological adaptations as central component of affective states (Norman et al., 2014). This link has frequently been proposed (Critchley et al., 2013; Preston & De Waal, 2002; Singer, 2006) and was further implied by the

involvement of brain regions of the CAN (Benarroch, 1993; Thayer & Lane, 2009) in empathy (Lamm et al., 2017). Regardless, the second empirical study of this thesis is among the first to investigate how a person's tendency to empathize with others is related to the extent of changes in heart rate when confronted with complex social stimuli. In line with the theoretical assumption, the extent of one's change in heart rate throughout the motion picture was positively correlated with the individual tendency for empathic concern measured by the IRI (Davis, 1983; Paulus, 2009). In specific emotive scenes, this association could be replicated, yet only when subgroups representing predominant response patterns were examined (i.e. 'tsunami' and 'family reunion'). These findings have further implications for current discussions regarding interindividual similarity (Golland et al., 2014) and the bodily component of empathy (de Waal & Preston, 2017).

First, the benefit of the cluster-analytic approach is substantiated by demonstrating that the correlation between self-reported empathic concern and the range of changes in heart rate during specific scene does only hold true if subgroups of homogeneous clusters are analysed. Since this correlation is concealed when merging data across different response patterns, the necessity to consider individually disparate heart rate trajectories is apparent.

Second, our findings are in line with the understanding of empathy as an 'embodied process' as de Waal and Preston (2017) describe it. However, this conclusion can only be drawn within limitations. Although changes in heart rate in the second empirical study correlated with participants' self-reported tendency for empathic concern, it cannot be ruled out whether also feelings of sympathy and prosocial concern, which would include a motivational component towards helping behaviour (Lamm et al., 2017), were present. Since psychophysiological adaptations occur with the goal to prepare the individual for its interaction with the environment (Levenson, 2014), sympathy and prosocial concern most likely contribute to the emergence of changes in heart rate throughout the motion picture. Analyses of discriminant validity of the IRI or its German version SPF and the discussed related concepts are still lacking to date. However, studies on brain activation related to sympathy indicated that this process relies on brain regions of the reward system (Singer & Klimecki, 2014), and therefore not direct involvement of brain regions of the CAN (Benarroch, 1993). Although this does not preclude our findings from being related to sympathy, and an overlap in active brain regions does not necessarily translate to an overlap in function (Zaki & Ochsner, 2012), it still suggests that the neural base of empathy is closer to processes of psychophysiological adaptations than sympathy. Furthermore, findings could stem from emotional contagion without self-other distinction (de Vignemont & Singer, 2006). Considering the study setting (i.e. wearing a

measurement garment, presence of study staff), mere emotional contagion with a loss of distinction between oneself and the actors on screen seems unlikely, but cannot be ruled out completely either.

Despite these limitations, findings from the second empirical study point out how vital it is to consider the possibility of interindividually disparate heart rate trajectories during emotional experiences when studying the psychophysiological facet of socio-cognitive functions. This appears to be especially important for complex emotive stimuli, which draw heavily upon one's individual evaluation and interpretation of the perceived situation (Adolphs, 2003) and thus allow for large interindividual differences in the top-down control of physiological adaptations (Smith et al., 2017). Furthermore, the second empirical study identified empathy as a first key factor linked to one's extent of psychophysiological adaptation, thus contributing to the discussion how personality traits shape our bodily adaptations to one's challenging social environment. Future studies need to recognize the potential for disparate psychophysiological responses to social stimuli in order to extend these initial findings.

7.1.3 What is the informative value of heart rate variability in social cognition?

Although the emergence and role of psychophysiological adaptations in emotions are interpreted vastly different in social neuroscience, their general importance is unquestioned (Gendron & Feldman Barrett, 2009). Regarding cardiac functions, consensus is reached for the relevance of changes in heart rate in response to emotive situational demands (Kreibig, 2010). More and more argumentative weight has been put on measures of HRV at rest lately (Laborde et al., 2017), yet the interpretation of HRV aside from its importance in physical health is inconclusive. Measures that characterize the beat-to-beat variability of one' heart functioning are strongly associated with morbidity and mortality related to cardiovascular pathologies (Kemp et al., 2017) and gained in popularity to predict a person's flexibility of autonomic and emotional regulatory capacities (Appelhans & Luecken, 2006). Conceptually, HRV has been interpreted as indicator for the efficiency with which regions of the CAN are able to adaptively regulate cardiac functions (Thayer & Lane, 2000), which makes it an attractive construct in research questions targeting social cognition. However, HRV appears to be at risk for becoming an umbrella framework at the expense of methodological and interpretative clarity.

So far, HRV at rest has been related to the inference of mental and affective states (Quintana et al., 2012), prosocial behaviour (Beffara et al., 2016) as well as perceptive and attentional functions in the processing of facial emotional expressions (Park & Thayer, 2014). However, this link between HRV and socio-cognitive functions has not been found consistently

(Muhtadie et al., 2015; Tracy & Giummarra, 2017) and could not be observed in the second empirical study of this thesis as well. No correlation between self-reported state and trait empathy and multiple measures of HRV in the time- and frequency domain could be found.

Three critical points need to be considered before leaping to conclusions. First, the multitude of measures that serve to quantify HRV (Laborde et al., 2017) increases the danger of fishing for significant results in case studies include more than one measure of HRV in their analysis. Second, HRV is influenced by health-related factors such as age or blood pressure (Laborde et al., 2017; Opthof, 2000). These factors need to be incorporated in statistical analyses. Otherwise, the interpretation of HRV is reduced to a global measure of one's general cardiovascular health (Kemp et al., 2017; Laborde et al., 2017). This could serve as an alternative explanation why measures of HRV frequently correspond to a person's cognitive abilities (Thayer et al., 2009) and would impede further conclusions. Third, current conceptual frameworks on HRV (Porges, 1995; Thayer & Lane, 2009) are characterized by a very broad and open phrasing and terminology, which makes it easy to integrate findings of any kind within the context of individual-environment interactions and goal-directed adaptations. These caveats need to be avoided to make HRV a useful measure and potential meaningful correlate of specific brain functions. Until further evidence substantiates the interpretation of HRV, conclusions should be drawn with caution.

7.2 Clinical implications

Findings of the current thesis can be related to clinical aspects of social cognition, yet the transfer from the empirical to the clinical context is limited by the designs of the two empirical studies. Both empirical studies presented in this thesis are based on paradigms during which participants were asked to passively perceive potentially emotive stimuli without further instructions. While the term "passive viewing" does not imply that participants were not actively involved in the processing of these stimuli, the study designs did not include overt behavioural responses of the participants in the actual emotive situation. As far as behavioural measures are included, they stem from self-reports providing information on their state and trait empathy in the second empirical study. Thus, no unbiased measure on the behavioural level is incorporated. Because of this limitation, results can be used to generate hypotheses regarding the behavioural consequences of the observed brain networks and psychophysiological processes, but it is not valid to assume that they necessarily translate to behaviour.

The first empirical study presented evidence that individuals with MTLE exhibit a widespread disruption of FC among brain regions implicated in the processing of facial

emotional expressions. This de-coupling within intrinsic functional networks is consistent with current studies on this subject (Broicher, Frings, et al., 2012; Doucet et al., 2013; Maccotta et al., 2013; Pittau et al., 2012) and further supports the definition of epilepsy as a disease of brain networks instead of single brain regions (Berg et al., 2010). The discovery that intrinsic functional networks are disrupted beyond the initially epileptogenic brain lesion is essential for the understanding why individuals with MTLE are often faced with cognitive deficits which rely on the orchestrated activity of multiple brain regions (Cataldi et al., 2013). Deficits in social cognition are a common finding in people with MTLE (Bora & Meletti, 2016; Broicher, Kuchukhidze, et al., 2012). Affected individuals are not only less accurate in the recognition of facial emotional expression (Broicher, Frings, et al., 2012; Monti & Meletti, 2015), but also show difficulties in the inference of mental states of others (Schacher, Haemmerle, et al., 2006; Stewart et al., 2016). The network alterations found in the first empirical study of this thesis can be a putative cause of these behavioural deficits. This seems especially plausible given the more extensive network disruption observed in right-sided MTLE in this study and coinciding worse performance in tests on social cognition in right-sided MTLE shown in behavioural studies (Bora & Meletti, 2016). Still, the differences in FC found in this thesis are far more extensive than the often only subtle differences on the behavioural level (e.g. Bonora et al., 2011). Potentially, compensatory network re-configurations, which have been discussed lately in studies on intrinsic FC (Bettus et al., 2009; Tracy & Doucet, 2015), could explain this difference between the neural and the behavioural level. However, alternative activation patterns, which could compensate for the functional de-coupling of the mesial temporal lobe, have not been reported in studies on facial emotion perception so far (Ives-Deliperi et al., 2017; Labudda et al., 2014; Schacher, Haemmerle, et al., 2006; Toller et al., 2015). Due to the analysis of FC among pre-specified ROIs in this thesis, compensatory changes in the network configuration cannot be studied with this approach. Therefore, studies combining analyses on intrinsic functional networks in combination with behavioural measures are necessary to address this issue.

The second empirical study portrayed the diversity of heart rate trajectories during emotional processing. The analyses revealed that changes in heart rate to complex social stimuli are rarely uniform, but rather vary in shape, temporal dynamics and extent among individuals. The presented approach offers two main implications for clinical work. First, the choice of stimulus material created an experimental setting which allowed participants to perceive social situations as life-like as possible while being standardized enough to compare psychophysiological responses among participants. Unlike many tests currently in clinical use

to assess socio-cognitive functions (Henry et al., 2016), our paradigm is able to evoke strong emotional experiences and was immersive enough that participants reported to empathize deeply with the protagonists. Without a doubt, such a time-consuming study procedure is not feasible in the general clinical routine. However, it can find application in clinical research to generate knowledge on psychophysiological responses of specific patient groups. Moreover, shorter paradigms with a similarly engaging storyline could be tailored to the functions that need to be assessed. First attempts in this direction have been made with measures such as 'The Awareness of Social Inference Test' (McDonald et al., 2003) or the 'Movie for the Assessment of Social Cognition' (Dziobek et al., 2006), yet the stimulus material does not offer continuous emotive stimulation in a coherent plot.

Second, the cluster-analytical approach makes room for more than an oversimplified distinction between "healthy" and "pathological" responses to emotive stimuli. Traditionally, one would compare the extent of heart rate changes between healthy individuals and individuals affected by a specific disease with the expectation to find exaggerated or attenuated responses in the clinical group. As is made evident by the diversity of heart rate trajectories, homogeneity of bodily responses is not even present in healthy individuals. Although the underlying nature of each trajectory remains speculative in this thesis, these differences likely emerge from interindividual differences in the perception and interpretation of the emotive stimuli (Brosch et al., 2010) in dependence of one's personality traits, previous experiences, present bodily and mental states, and individual goals (Barrett, 2016; Critchley et al., 2013; Levenson, 2014; Norman et al., 2014). As a consequence, objectively equal stimulation with emotive material is accompanied by vastly different bodily responses. Therefore, any comparison of mean heart rate responses between groups would be futile. Alternatively, it is possible to examine if individuals with a specific pathology correspond to a specific subgroup of a healthy control group or whether individuals sharing the same conditions would form a subgroup of their own. This might even be useful to identify individuals with deviant physiological responses that could be overlooked otherwise. Behavioural studies in MTLE showed that individual deficits in social cognition can be concealed by group-wise comparisons but become apparent when considering each individual's performance (Bonora et al., 2011; Meletti et al., 2009). Equally, individual trajectories of physiological signals could be analysed by the methodological approach of the second empirical study.

7.3 Limitations and outlook

A general limitation of the two presented empirical studies is the restricted use of behavioural measures. Aside from self-report questionnaires on trait and state empathy in the second empirical study, no further questionnaires or procedures that require overt behavioural responses were applied. In the first empirical study, behavioural data from participants with MTLE was not available due to the recruitment of participants from the pre-surgical diagnostic procedure of the Swiss Epilepsy Centre in Zurich. Hence, neuropsychological data were not available for all participants and prohibited further analyses regarding the behavioural relevance of the found network alterations. In the second empirical study, this limitation was accepted during the design of the study procedure in favour of an unperturbed assessment of changes in heart rate. Interrupting the presentation of the motion picture in order to obtain self-reports or ratings concerning specific scenes would have influenced the processing of subsequent scenes and would have disrupted the cinematic atmosphere, which allowed participants to become immersed in the plot. At least, the individual rating taking place after the motion picture, which targeted emotional experiences, feelings of empathy and bodily changes during the presentation, was valuable to demonstrate a link between changes in heart rate and the subjective experience during the motion picture. Still, these self-report measures most likely are subject to various sources of bias such as social desirability and the image of oneself that participants aimed to express (Choi & Pak, 2005; Fisher & Katz, 2000). One could speculate that recordings of physiological signals in response to emotive content could bring forth more valid estimates of empathy. However, the absence of physiological responses cannot be equated to the absence of emotional processes, and strong physiological responses are not necessarily indicative of strong emotions (Bermond, Nieuwenhuysedr, Fasotti, & Schuerman, 1991; Kreibig, 2010; Laird & Lacasse, 2014). Additionally, top-down processes permit partial control of the CNS over cardiac functions (Thayer & Lane, 2000). Therefore, measures of psychophysiological responses should be treated as complementary information but not as fully objective and bias-free indicators of emotional processes.

A second limitation arises from the applied stimulus material. The application of dynamic fearful faces in the first empirical study and the presentation of an entire motion picture in the second empirical study already are a progress compared to frequently applied paradigms with static images (Henry et al., 2016). However, participants remain in the position of a spectator instead of being actively involved in social interactions. Because of this third-person perspective, it remains unclear how findings translate to real-life social interactions in which it is not sufficient to merely observe others, but ongoing adequate behavioural responses are

necessary to maintain the social exchange. This "spectatorial gap" between current research and real social behaviour has been addressed by Schilbach et al. (2013), who point out how being actively involved in social interaction requires different socio-cognitive functions than simply observing social encounters as a detached spectator. Evidently, such an interaction cannot take place while watching a motion picture, yet the extensive background information provided on the characters facilitate the emotional engagement with the actions on screen and allowed participants to form a (one-sided) bond with the characters. Nonetheless, the element of active interaction needs to be addressed by future studies.

A potential application within the medical care of MTLE can be derived from the results of the first empirical study. Analyses of FC are lately gaining relevance in the pre-surgical evaluation of patients and might provide a cognitively less demanding way to examine neural circuits of patients (Pittau et al., 2014; Pittau & Vulliemoz, 2015; Tracy & Doucet, 2015). Since intrinsic functional networks and networks observed during task states overlap to a high degree (Cole et al., 2014; Fair et al., 2007), the extensive preparation and practicing of tasks which patients need to perform during the fMRI session could be omitted. While the application of intrinsic FC is not yet as far developed and implemented to replace task-related fMRI in the clinical setting completely, the results of this thesis support the comparability of the two approaches. As a limiting factor, data for the current study was not collected during a task-free state but during the perception of dynamic fearful faces. Regression of the task-related signal converted the individual time series in a way that allowed us to infer intrinsic FC regardless (Fair et al., 2007), though possible modulation of the observed network configuration by the task has to be taken into account (Cole et al., 2014; Gonzalez-Castillo & Bandettini, 2017). Despite this limitation, analysing intrinsic FC among brain regions showed that functional alterations can not only be found in paradigms involving active engagement in a specific task, but also in the absence of a task. This finding should encourage further studies on the convergence of task-free and task-related fMRI examinations in other cognitive domains. Additionally, results of studies on intrinsic FC need to be related to behavioural data in order to evaluate their clinical relevance.

A combination of these findings from the first empirical study and the innovative study design of the second empirical study could be especially fruitful in research on MTLE. In people with MTLE, deficits in social cognition (Bora & Meletti, 2016) coincide with structural (Keller et al., 2015) and functional (Caciagli et al., 2014) brain alterations that comprise core regions of the CAN (Benarroch, 1993). These brain lesions already imply altered regulatory activity of the CNS on the ANS. In line with this assumption, changes in heart rate and HRV are not only

a frequent feature of seizures originating from the mesial temporal lobe (Saleh et al., 2000; Sevcencu & Struijk, 2010), but are also found in time periods in between seizures (Lotufo et al., 2012). Possibly, functional network alterations as revealed in MTLE in this thesis find expression on the behavioural but also on the physiological level. So far, research on cardiac functions in MTLE is mostly restricted to ECG recordings during clinical assessments (Sevcencu & Struijk, 2010), thus giving little insight into the behavioural relevance of these altered cardiac functions. Applying the experimental setting of the second empirical study in a study including individuals with MTLE can deepen the understanding of socio-cognitive deficits in this clinical population.

7.4 Conclusion

Initiated by the paramount importance of social cognition for social integration, the overarching goal of this thesis was to portray neural and psychophysiological facets of socio-cognitive functions. By adopting a network perspective, the current results show how the perception of social signals relies on widespread brain networks which involve regions implicated in emotional processing as well as autonomic regulation. The susceptibility of these networks to mesial temporal lesions in the course of MTLE deepens our understanding of epilepsy as a network disease and provide a putative cause for socio-cognitive deficits in MTLE. Furthermore, the importance of autonomic functions was demonstrated by studying changes in heart rate to examine the bodily component of social cognition with special focus on empathy. The discovery that diversity of cardiac responses to social situations is the rule rather than the exception has important implications for future studies not only in the clinical context but in research on psychophysiology in general. In sum, the presented work encourages a multimodal approach towards social cognition which respects that complex intraindividual functional networks can lead to interindividual diversity on the neural, physiological and behavioural level.

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